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(57) Abstract

Platelet activating factor receptor antagonists of diverse structures are imparted with 5-lipoxygenase activity by adding a moiety such as a hydroxamate, hydroxyurea, oxalkane, thioalkane, quinolylmethoxy, or amidohydroxyurea to the PAF receptor antagonist at a position on the PAF antagonist molecule that demonstrates "bulk tolerance", i.e., the ability to accommodate functionality without the significant loss of PAF activity.

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DUAL FUNCTIONAL ANTI-INFLAMMATORY AND IMMUNOSUPPRESSIVE AGENTS

This invention is in the area of pharmaceutical compositions and methods for the treatment of inflammatory and immune disorders, and specifically provides novel compounds that have PAF receptor antagonist activity and inhibit the enzyme 5-lipoxygenase.

Platelet activating factor (PAF, 1-O-alkyl-2-acetyl-sn-glycerol-3-phosphorylcholine) is a potent inflammatory phospholipid mediator with a wide variety of biological activities. PAF was initially identified as a water soluble compound released by immunoglobulin E (IgE)-sensitized rabbit basophils. It is now known that PAF is also generated and released by monocytes, macrophages, polymorphonuclear leukocytes (PMNs), eosinophils, neutrophils, natural killer lymphocytes, platelets and endothelial cells, as well as by renal and cardiac tissues under appropriate immunological and non-immunological stimulation. (Hwang, "Specific receptors of platelet-activating factor, receptor heterogeneity, and signal transduction mechanisms", Journal of Lipid Mediators 2, 123 (1990).) PAF causes the aggregation and degranulation of platelets at very low concentrations. The potency (active at 10^{-12} to 10^{-9}M), tissue level (picomoles) and short plasma half life (2-4 minutes) of PAF are similar to those of other lipid mediators such as thromboxane A_2, prostaglandins, and leukotrienes.

PAF mediates biological responses by binding to specific PAF receptors found in a wide variety of cells and tissues. Structure-activity studies on PAF and its analogs indicate that the ability of PAF to bind to these receptors is highly structure specific and stereospecific. (Shen, et al., "The Chemical and Biological Properties of PAF Agonists, Antagonists, and Biosynthetic

Inhibitors", Platelet-Activating Factor and Related Lipid Mediators, F. Snyder, Ed. Plenum Press, New York, NY 153 (1987)). While PAF mediates essential biological responses, it also appears to play a role in pathological immune and inflammatory responses. Many published studies have provided evidence for the involvement of PAF in human diseases, including arthritis, acute inflammation, asthma, endotoxic shock, pain, psoriasis, ophthalmic inflammation, ischemia, gastrointestinal ulceration, myocardial infarction, inflammatory bowel diseases, and acute respiratory distress syndrome. Animal models also demonstrate that PAF is produced or increased in certain pathological states.

The involvement of PAF in pathological inflammatory and immune states has stimulated a substantial research effort to identify PAF receptor antagonists. In 1983, a phospholipid analog referred to as CV-3988 (*rac*-3-(N-n-octadecyl-carbamoyloxy-θ-methoxypropyl-2-thiazolioethyl phosphate) was reported to have PMF receptor antagonist properties. (Terashita, et al., Life Sciences **32**, 1975 (1983).) In other early work in this area, Shen, et al., (in Proc. Natl. Acad. Sci. (U.S.A.) **82**, 672 (1985)), reported that kadsurenone, a neolignan derivative isolated from Piper fotukadsura Sieb et Zucc (a Chinese herbal plant) was a potent, specific and competitive inhibitor of PAF activity at the receptor level.

Since then, a number of compounds of diverse chemical structure have been identified as PAF receptor antagonists. Examples of active hetrazepines are disclosed in European Patent Application No. 338 993 A; Ger. Offen. DE 3,936,828; Ger. Offen. DE 4,006,471; Ger. Offen.

DE 3,701,344; Ger. Offen. DE 3,724,164; Ger. Offen. DE 3,724,031; U.S. Patent No. 4,959,361; European Patent Application No. 0 407 955 A1; and European Patent Application No. 0 367 110. A number of imidazo[2.1-a]isoquinolines with PAF receptor antagonist activity are also known, including those disclosed in United States Patent Nos. 4,910,206 and 4,992,428. Pyrrolo[1,2-c]thiazoles with PAF receptor antagonist activity are disclosed, for example, in Lave et al., Drugs of the Future, 14(9), 891 (1989); European Patent Application No. 388 309 A2; and European Patent Application No. 0 252 823 A1. Thiazolidinecarboxamides with PAF inhibiting activity are disclosed in U.S. Patent No. 4,987,132.

A number of 2,5-diaryl tetrahydrofurans with PAF receptor antagonist activity are disclosed in U.S. Patent Nos. 4,996,203, 5,001,123 and 4,539,332 to Biftu, *et al.* ; European Patent Application Nos. 89202593.3, 90306235.4, and 90306234.7; Journal of Biological Chemistry 260(29), 15639 (1985); and J. Pharmacol. Ther. 246, 534-541 (1988).

Leukotrienes, like PAF, are potent local mediators, playing a major role in inflammatory and allergic responses, including arthritis, asthma, psoriasis, and thrombotic disease. Leukotrienes are straight chain eicosanoids produced by the oxidation of arachidonic acid by lipoxygenases. Arachidonic acid is oxidized by 5-lipoxygenase to the hydroperoxide 5-hydroperoxyeicosatetraenoic acid (5-HPETE), that is converted to leukotriene A_4, that in turn can be converted to leukotriene B_4, C_4, or D_4. The slow-reacting substance of anaphylaxis is now known to be a mixture of leukotrienes C_4, D_4, and E_4, all of which are potent bronchoconstrictors. There has been a research effort to develop

specific antagonists or inhibitors of leukotriene synthesis, to prevent or minimize pathogenic inflammatory responses mediated by these compounds.

Leukotrienes are released simultaneously from leukocytes with PAF, possibly from a common phospholipid precursor such as 1-O-hexadecyl-2-arachidonyl-sn-glycero-phosphocholine, and upon cellular activation, act synergistically with PAF in many biological models. PAF and leukotrienes have been together associated with disease states such as asthma, arthritis, psoriasis, inflammatory bowel disease, and other inflammatory and immunological disorders.

To date, only a few functionalities have been demonstrated to consistently inhibit the enzyme 5-lipoxygenase. European Patent Application Nos. 90117171.0 and 901170171.0 disclose indole, benzofuran, and benzothiphene lipoxygenase inhibiting compounds. Recently, it was reported that the tetrahydrothiophene derivative of L-652,731, trans-2,5-bis-(3,4,5-trimethoxyphenyl)-tetrahydrothiophene (L-653,150), is a potent PAF antagonist and a moderate inhibitor of 5-lipoxygenase. (Biftu, et al, Abstr. of 6th Int. Conf. on Prostaglandins and Related Compounds, June 3-6, 1986, Florence, Italy; U.S. Patent No. 4,757,084 to Biftu.)

Given the significant number of pathological immune and inflammatory responses that are mediated by PAF and leukotrienes, there remains a need to identify new compounds and compositions that exhibit PAF receptor antagonist activity and inhibit the enzyme 5-lipoxygenase.

Therefore, it is an object of the present invention to provide compounds that act as PAF receptor antagonists and also inhibit the enzyme 5-lipoxygenase.

It is another object of the present invention to provide pharmaceutical compositions for the treatment of pathological immune or inflammatory disorders mediated by PAF or products of 5-lipoxygenase.

It is another object of the present invention to provide a method for the treatment of pathological immune or inflammatory disorders mediated by PAF or products of 5-lipoxygenase.

Summary of the Invention

It has been discovered that compounds with PAF receptor antagonist activity can be imparted with 5-lipoxygenase inhibiting activity by the addition of R^1 to a bulk tolerating location on the compound, wherein R^1 is:

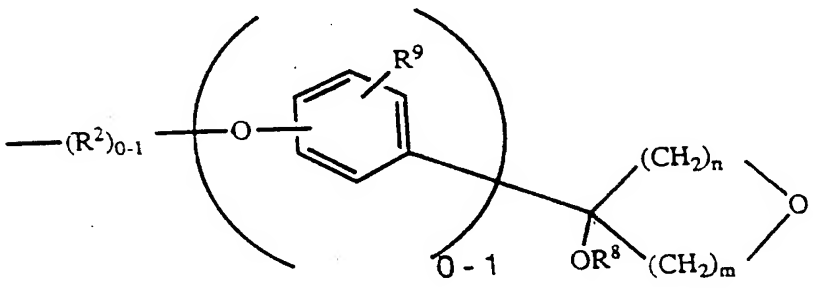
(1) a hydroxamate or hydroxyurea of the formula:

$-R^2N(OM)C(O)N(R^3)R^4$, $-R^2N(R^3)C(O)N(OM)R^4$,
$-R^2N(OM)C(O)R^4$, $-R^2C(O)N(OM)R^4$, $-N(OM)C(O)N(R^3)R^4$,
$-N(R^3)C(O)N(OM)R^4$, $-N(OM)C(O)R^4$, or $-C(O)N(OM)R^4$;

(2) an amidohydroxyurea of the formula:

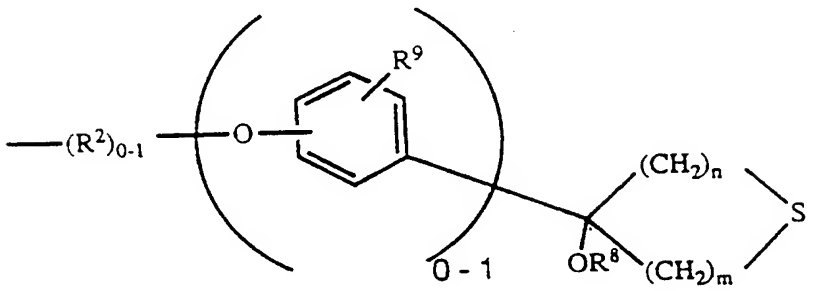
$-N(R^8)C(O)C(R^8)N(OM)C(O)NHR^9$,
$-C(O)N(R^8)C(R^8)N(OM)C(O)NHR^9$,
$-R^2N(R^8)C(O)C(R^8)N(OM)C(O)NHR^9$,
$-R^2C(O)N(R^8)C(R^8)N(OM)C(O)NHR^9$,
$-NHC(O)N(OM)C(R^8)C(O)N(R^8)_2$; or
$-NHC(O)N(OM)C(R^8)N(R^8)C(O)R^8$;

(3) an oxalkane of the structure:

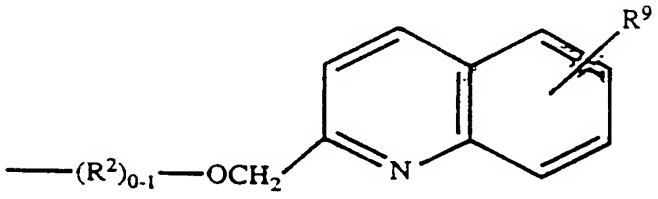


wherein n and m are independently 1-4 ;

(4) a thioalkane of the structure:



or (5) a quinolylmethoxy of the structure:



R^2 is alkyl, alkenyl, alkynyl, alkyaryl, aralkyl, halo lower alkyl, halo lower alkenyl, halo lower alkynyl, $-C^{1-10}$alkyl(oxy)C^{1-10}alkyl, $-C^{1-10}$alkyl(thio)C^{1-10}alkyl, $-N(R^3)C(O)$alkyl, $-N(R^3)C(O)$alkenyl, $-N(R^3)C(O)$alkynyl, $-N(R^3)C(O)$(alkyl)oxy(alkyl), $-N(R^3)C(O)$(alkyl)thio(alkyl), $-N(R^3)C(O)N$(alkyl), $-N(R^3)C(O)N$(alkenyl), $-N(R^3)C(O)N$(alkynyl), $-N(R^3)C(O)N$(alkyl)oxy(alkyl), $-N(R^3)C(O)N$(alkyl)thio(alkyl), $-N(R^3)C(O_2)$alkyl, $-N(R^3)C(O_2)$alkenyl, $-N(R^3)C(O_2)$alkynyl, $-N(R^3)C(O^2)$(alkyl)oxy(alkyl), $-N(R^3)C(O_2)$(alkyl)thio(alkyl), $-OC(O_2)$alkyl, $-OC(O_2)$alkenyl, $-OC(O_2)$alkynyl, $-OC(O_2)$(alkyl)oxy(alkyl), $-OC(O_2)$(alkyl)thio(alkyl), $-N(R^3)C(S)$alkyl, $-N(R^3)C(S)$alkenyl, $-N(R^3)C(S)$alkynyl, $-N(R^3)C(S)$(alkyl)oxy(alkyl),

$-N(R^3)C(S)(alkyl)thio(alkyl)$, $-N(R^3)C(S)N(alkyl)$, $-N(R^3)C(S)N(alkenyl)$, $-N(R^3)C(S)N(alkynyl)$, $-N(R^3)C(S)N(alkyl)oxy(alkyl)$, $-N(R^3)C(S)N(alkyl)thio(alkyl)$, $-N(R^3)C(S)S(alkyl)$, $-N(R^3)C(S)S(alkenyl)$, $-N(R^3)C(S)S(alkynyl)$, $-N(R^3)C(S)S(alkyl)oxy(alkyl)$, $-N(R^3)C(S)S(alkyl)thio(alkyl)$, $-SC(S)S(alkyl)$, $-SC(S)S(alkenyl)$, $-SC(S)S(alkynyl)$, $-SC(S)S(alkyl)oxy(alkyl)$, or $-SC(S)S(alkyl)thio(alkyl)$;

R^3 and R^4 are independently alkyl, alkenyl, alkynyl, aryl, aralkyl, alkyaryl, hydrogen, C_{1-6} alkoxy-C_{1-10} alkyl, C_{1-6} alkylthio-C_{1-10} alkyl, and C_{1-10} substituted alkyl (wherein the substituent is independently hydroxy or carbonyl, located on any of C_{1-10});

R^8 is H, lower alkyl, or lower alkenyl;

R^9 is H, halogen, lower alkoxy, or lower alkyl; and

M is hydrogen, a pharmaceutically acceptable cation, or a metabolically cleavable leaving group.

The resulting compounds act as "dual function antagonists" in that they retain PAF receptor antagonist activity and also inhibit the enzyme 5-lipoxygenase. The invention described herein provides a novel route to the enhancement of utility of conventional PAF antagonists and 5-lipoxygenase inhibitors.

According to the invention, known PAF antagonists of diverse structures are imparted with 5-lipoxygenase activity by adding an iron chelating group such as the above-defined hydroxamate or hydroxyurea groups; or oxalkane, thioalkane, quinolylmethoxy, or amidohydroxyurea moieties to the PAF antagonist at a position on the PAF antagonist molecule that demonstrates "bulk

tolerance", i.e., the ability to accommodate functionality without the loss of PAF activity. The R^1 group is added to the PAF receptor antagonist through conventional means, including by appropriate derivatization of amino or carboxylic acid groups positioned such that the 5-LO inhibiting moiety does not significantly affect the PAF receptor antagonist activity of the molecule. With the aid of molecular modeling, the 5-lipoxygenase inhibiting moiety is optimally oriented for the substrate binding domain of 5-lipoxygenase. The length and lipophilicity of the side chain or spacer (R^2) between the aromatic hydrophobic core of the PAF antagonist and the 5-lipoxygenase inhibiting moiety is optimized by conventional means, including by evaluation of standard structure-activity relationships.

In another embodiment of this invention, the utility of known PAF receptor antagonists is enhanced by the addition of substituted pyridinium heterocycles or other quaternary N-heterocycles of the formula $-OR^6N(R^5)R^6-(C_5H_4N)R^6R^7$, $-OR^6N(CO_2R^5)R^6-(C_5H_4N)R^6R^7$, $-OR^6N(COR^5)R^6-(C_5H_4N)R^6R^7$, $-OR^6OC(O)N(COR^5)R^6-(C_5H_4N)R^6R^7$, $-OR^6O(CO)N(CO_2R^6)R^6(C_5H_4N)R^6R^7$, or $-R^2(C_5H_4N)R^6R^7$, wherein

R^5 is lower alkyl, lower alkenyl, lower alkynyl, hydroxyl, hydrogen, halo lower alkyl, halo lower alkenyl, halo lower alkynyl, aralkyl, or aryl;

R^6 is lower alkyl, lower alkenyl, lower alkynyl, aralkyl, halo lower alkyl, halo lower alkenyl, halo lower alkynyl, or aryl; and

R^7 is an organic or inorganic anion.

These quaternized heterocycles increase the water solubility of the PAF receptor antagonist, allowing the compound to be administered by injection or

infusion intravenously. Further, the addition of the substituted pyridinium heterocycle or other quaternary N-heterocycle to the PAF antagonist in many cases enhances the PAF antagonist activity of the compound.

In the circumstance that the addition of R^1 decreases the PAF receptor antagonist activity of the conventional agent being modified, PAF antagonist activity may be restored, or augmented, by the addition of a substituted pyridinium heterocycle or other quaternary N-heterocycle to an appropriate position on the molecule.

A method to treat disorders mediated by PAF or leukotrienes is also disclosed, that includes administering an effective amount of one or more of the compounds described herein or a pharmaceutically acceptable salt or derivative thereof, optionally in a pharmaceutically acceptable carrier.

The compounds disclosed herein can also be used as research tools to study the structure and location of PAF receptors as well as biological pathways involving leukotrienes.

Brief Description of the Figures

Figure 1 is a schematic illustration of PAF receptor antagonist hetrazepines modified to exhibit 5-lipoxygenase inhibiting activity. R^{10} is hydrogen, alkyl, aryl, alkoxy, nitro, halogen, amino, alkylamino, dialkylamino, arylamino, diarylamino, heteroarylamino, diheteroarylamino. R^{11} is hydrogen or alkyl.

Figure 2 is a schematic illustration of PAF receptor antagonist dimethoxyphenylethyl-phenylimidazo-[2.1-a]isoquinolines modified to exhibit 5-lipoxygenase inhibiting activity.

Figure 3 is a schematic illustration of PAF receptor antagonist pyrrolo[1,2]thiazoles modified to exhibit 5-lipoxygenase inhibiting activity. R^{12} is H, alkyl, aryl, or aralkyl.

Figure 4 is a schematic illustration of PAF receptor antagonist thiazolidinecarboxamides

modified to exhibit 5-lipoxygenase inhibiting activity.

Figure 5 is a schematic illustration of PAF receptor antagonist dihydropyridines modified to exhibit 5-lipoxygenase inhibiting activity.

Figure 6 is a schematic illustration of PAF receptor antagonist propenylcarboximides modified to exhibit 5-lipoxygenase inhibiting activity.

Figures 7 and 7a are schematic illustrations of PAF receptor antagonist kadsurenone analogs modified to exhibit 5-lipoxygenase inhibiting activity.

Figure 8 is a schematic illustration of 1,5-dioxabicyclo-[3.3.0]octanes with PAF receptor antagonist and 5-lipoxygenase inhibiting activity.

Detailed Description of the Invention

The term alkyl, as used herein, unless otherwise specified, refers to a saturated straight, branched, or cyclic hydrocarbon of C_1 to C_{10}.

The term lower alkyl, as used herein, and unless otherwise specified, refers to a C_1 to C_6 saturated straight, branched, or cyclic (in the case of C_{5-6}) hydrocarbon, and specifically includes methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, cyclopentyl, isopentyl, neopentyl, hexyl, isohexyl, cyclohexyl, 3-methylpentyl, 2,2-dimethylbutyl, and 2,3-dimethylbutyl.

The term alkenyl, as referred to herein, and unless otherwise specified, refers to a straight, branched, or cyclic (in the case of C_{5-6}) hydrocarbon of C_2 to C_{10} with at least one double bond.

The term lower alkenyl, as referred to herein, and unless otherwise specified, refers to

an alkenyl group of C_2 to C_6, and specifically includes vinyl, and allyl.

The term lower alkylamino refers to an amino group that has one or two lower alkyl substituents.

The term alkynyl, as referred to herein, and unless otherwise specified, refers to a C_2 to C_{10} straight or branched hydrocarbon with at least one triple bond.

The term lower alkynyl, as referred to herein, and unless otherwise specified, refers to a C_2 to C_6 alkynyl group, specifically including acetylenyl and propynyl.

The term aryl, as used herein, and unless otherwise specified, refers to phenyl or substituted phenyl, wherein the substituent is halo lower alkoxy or lower alkyl.

The term alkoxy, as used herein, and unless otherwise specified, refers to a moiety of the structure -O-alkyl.

The term heteroaryl, as used herein, and unless otherwise specified, refers to an aromatic moiety that includes at least one sulfur, oxygen, or nitrogen in the aromatic ring. Nonlimiting examples are furyl, pyridyl, pyrimidyl, thienyl, isothiazolyl, imidazolyl, tetrazolyl, pyrazinyl, benzofuranyl, benzothiophenyl, quinolyl, isoquinolyl, benzothienyl, isobenzofuryl, pyrazolyl, indolyl, isoindolyl, benzimidazolyl, purinyl, carbozolyl, oxazolyl, thiazolyl, isothiazolyl, 1,2,4-thiadiazolyl, isooxazolyl, pyrrolyl, pyrazolyl, quinazolinyl, pyridazinyl, pyrazinyl, cinnolinyl, phthalazinyl, quinoxalinyl, xanthinyl, hypoxanthinyl, pteridinyl, 5-azacytidinyl, 5-azauracilyl, triazolopyridinyl, imidazolopyridinyl, pyrrolopyrimidinyl, and pyrazolopyrimidinyl.

The term halo, as used herein, includes fluoro, chloro, bromo, and iodo.

The term halo lower (alkyl, alkenyl, or alkynyl) refers to a lower (alkyl, alkenyl, or alkynyl) group in which at least one of the hydrogens in the group has been replaced with a halogen atom.

The term aralkyl refers to an aryl group with an alkyl substituent.

The term alkaryl refers to an alkyl group that has an aryl substituent.

The term organic or inorganic anion refers to an organic or inorganic moiety that carries a negative charge and can be used as the negative portion of a salt, and in particular, an organic salt such as an organic amine, including a quaternary amine.

The term "pharmaceutically acceptable cation" refers to an organic or inorganic moiety that carries a positive charge and that can be administered in association with a pharmaceutical agent, for example, as a countercation in a salt.

The term "metabolically cleavable leaving group" refers to a moiety that can be cleaved <u>in vivo</u> from the molecule to which it is attached, and includes but is not limited to an organic or inorganic anion, a pharmaceutically acceptable cation, acyl (for example C(O)-alkyl, ncluding acetyl, propionyl, butryl, and succinyl) alkyl, phosphate, sulfate, and sulfonate.

The term "enantiomerically enriched composition or compound" refers to a composition or compound that includes at least 95% by weight of a single enantiomer of the compound.

The term PAF receptor antagonist refers to a compound that binds to a PAF receptor with a binding constant of 10 μM or lower.

The term 5-lipoxygenase inhibitor refers to a compound that inhibits the enzyme at 10 μM or lower in a broken cell system.

The term pharmaceutically active derivative refers to any compound that upon administration to the recipient, is capable of providing directly or indirectly, the compounds disclosed herein.

I. Structure and Synthesis of the Active Compounds

A. General Procedure for Synthesis of Hydroxyurea and Hydroxamate 5-Lipoxygenase Inhibiting Moieties

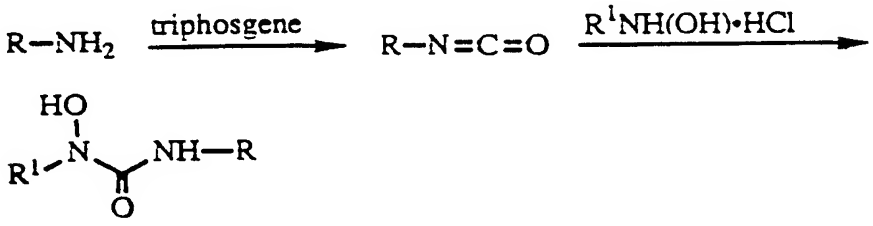
In one embodiment, compounds with PAF activity can be modified to impart 5-lipoxygenase activity to the compound by the addition of a group that has a hydroxamic acid function (-N(OH)C(O)-) or a hydroxyurea function (-N(OH)C(O)NH-). The hydroxamic acid or hydroxyurea function can be attached to the PAF antagonist molecule through a wide variety of means known or readily ascertainable to those of skill in the art of organic synthesis. For example, amines on the PAF antagonist molecule can be converted to hydroxyureas by known procedures, as described in more detail below. Carboxylic acids or carboxylic acid derivatives or precursors can easily be converted into hydroxamic acids.

Alternatively, other groups on the PAF antagonist molecule can be converted by standard techniques into amine or carboxylic acid functions that, in turn, can be converted into a hydroxyurea or hydroxamic acid, respectively.

The hydroxamic acid and hydroxyurea moieties can be attached to the PAF antagonist molecule through either end of the moiety; i.e., hydroxamic acids (-N(OH)C(O)-) can be attached through the carbonyl or the nitrogen (referred to

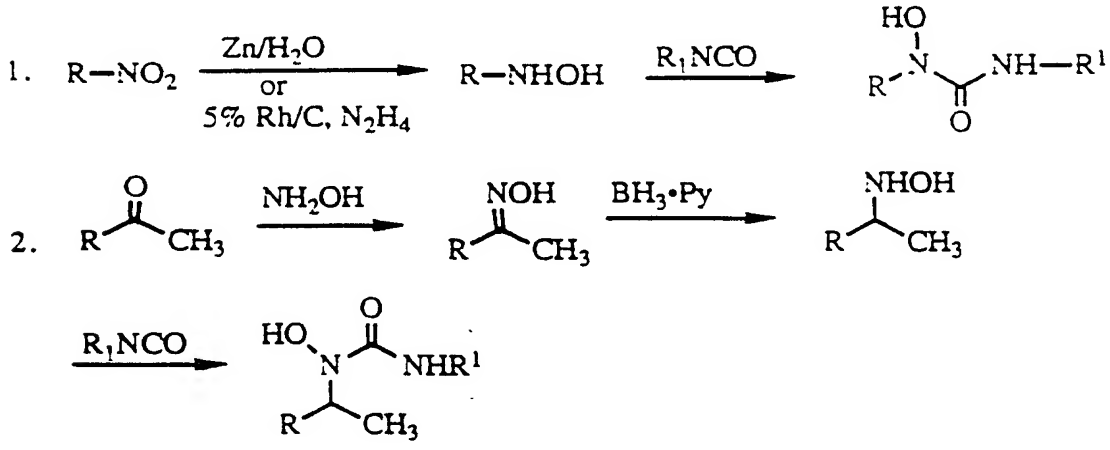
below as a "reverse" hydroxamic acid), and hydroxyureas (-N(OH)C(O)NH-) can be attached through the N(H) or N(OH) (referred to below as a "reverse" hydroxyurea) moiety.

A general procedure for preparing a hydroxyurea is:

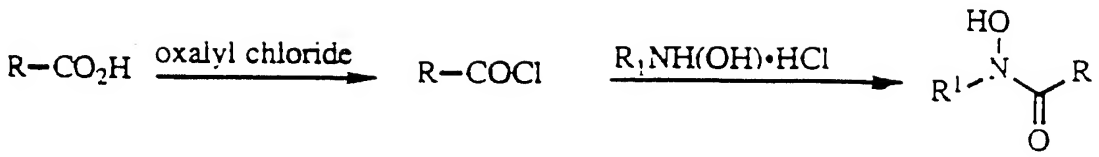


wherein R is a PAF receptor antagonist with or without a linking moiety, and R' is a moiety as defined in detail above.

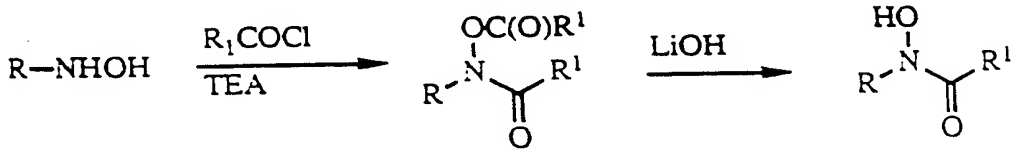
A general procedure for preparing a reverse hydroxyurea is:



A general procedure for preparing a hydroxamic acid is:



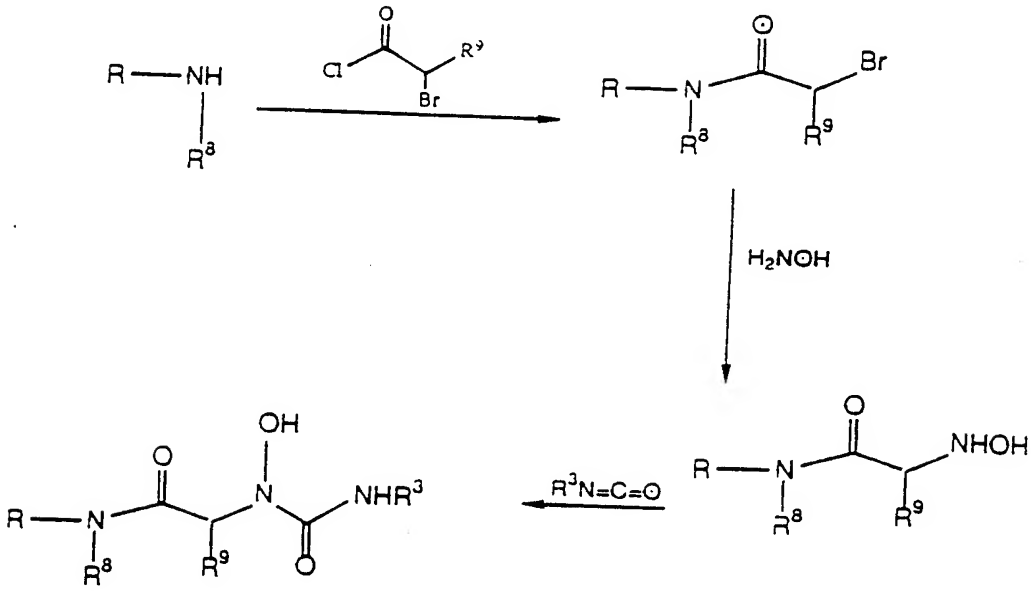
A general procedure for preparing a reverse hydroxamic acid is:



B. General Procedure for Synthesis of Amidohydroxyurea 5-Lipoxygenase Inhibiting Moieties

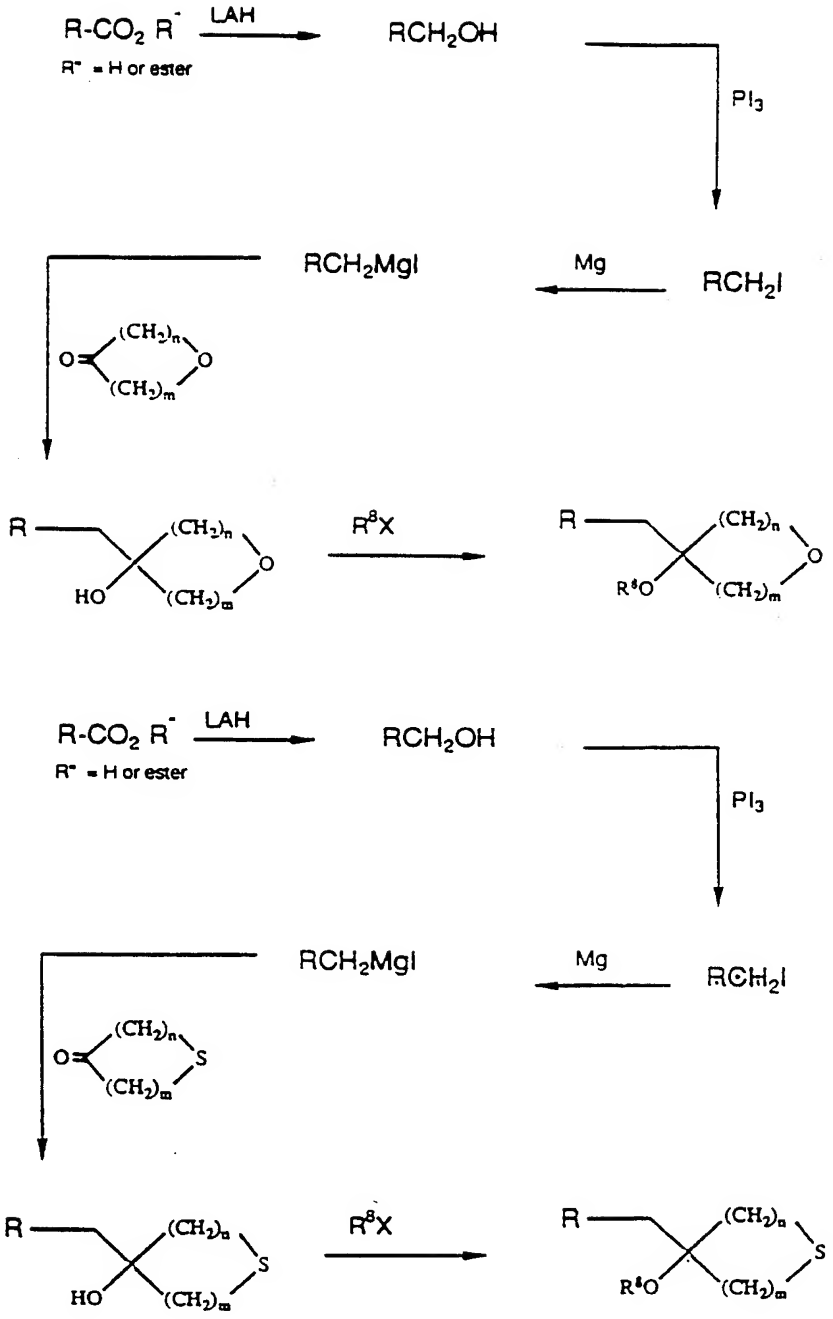
In a second embodiment, compounds with PAF activity can be modified to impart 5-lipoxygenase activity to the compound by the addition of a group that has an amidohydroxyurea moiety such as
$-N(R^8)C(O)C(R^8)N(OM)C(O)NHR^9$,
$-C(O)N(R^8)C(R^8)N(OM)C(O)NHR^9$,
$-R^2N(R^8)C(O)C(R^8)N(OM)C(O)NHR^9$,
$-R^2C(O)N(R^8)C(R^8)N(OM)C(O)NHR^9$,
$-NHC(O)N(OM)C(R^8)C(O)N(R^8)_2$; or
$-NHC(O)N(OM)C(R^8)N(R^8)C(O)R^8$.
The amidohydroxyurea moiety can be attached to the PAF antagonist molecule through a wide variety of means readily ascertainable to those of skill in the art of organic synthesis. The amidohydroxyurea moiety can be attached to the PAF receptor antagonist molecule through a spacer, R^2, as desired.

A general procedure for preparing amidohydroxyurea moieties is:

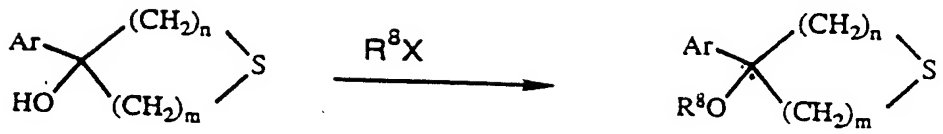


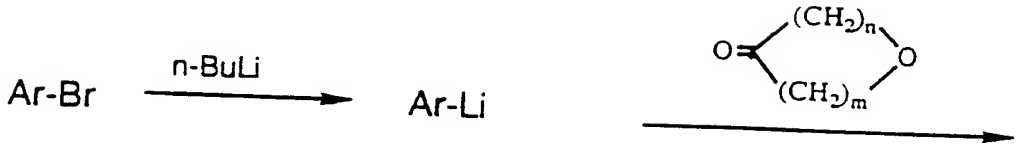
C. General Procedure for Synthesis of Oxaalkane and Thioalkane 5-Lipoxygenase Inhibiting Moieties

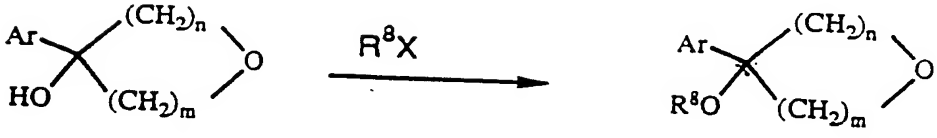
Oxaalkanes and thioalkanes can be prepared as described by Crawley, et al., J. Med. Chem., 35, 2600-2609 (1992), and illustrated below, by conversion of the PAF receptor antagonist into a Grignard reagent or lithium salt, followed by reaction with the appropriate cyclic ketone.


R-CO2 R'
LAH
R' = H or ester
RCH2OH
PI3
RCH2I
Mg
RCH2MgI
(CH2)n
(CH2)m
R
HO
R8X
R8O
R-CO2 R'
LAH
R' = H or ester
RCH2OH
PI3
RCH2I
Mg
RCH2MgI
S
R
HO
R8X
R8O


Ar-Br
n-BuLi
Ar-Li
(CH2)n
O
S
(CH2)m

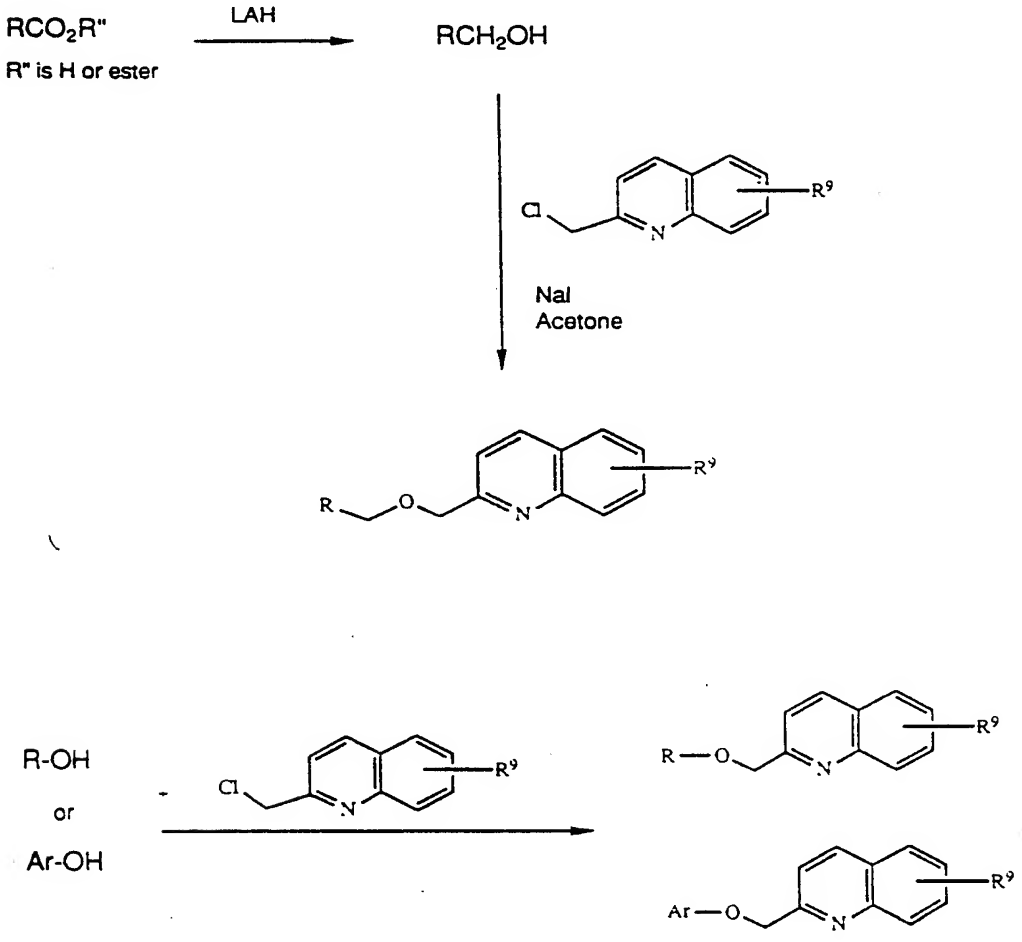

Ar
HO
(CH2)n
S
(CH2)m
R8X
Ar
R8O
(CH2)n
S
(CH2)m


Ar-Br
n-BuLi
Ar-Li
(CH2)n
O
O
(CH2)m


Ar
HO
(CH2)n
O
(CH2)m
R8X
Ar
R8O
(CH2)n
O
(CH2)m

D. **General Procedure for Synthesis of Quinolylmethoxy 5-Lipoxygenase Inhibiting Moieties**

Quinolylmethoxy moieties can be prepared as described by Musser, et al., J. Med. Chem., 35, 2501-2524 (1992), and references cited therein, as illustrated below.



E. Compounds with PAF Antagonist Activity

Any compound that has PAF receptor antagonist activity can be modified according to the present invention to impart 5-lipoxygenase inhibiting activity to that compound. It is generally known that there are locations on biologically active molecules, including PAF receptor antagonists active, that cannot be modified without compromising the desired biological activity. It is also generally known that there are locations on biologically active compounds that can tolerate the addition of moieties without significant loss of the desired biological activity. These areas of the compounds are referred to as "bulk tolerating" locations.

In another embodiment, the invention is a method to impart 5-lipoxygenase inhibiting activity to PAF receptor antagonists other than 2,4-diaryl-1,3-dithiolanes; 2,4-diaryl-1,3-dioxolanes; 2,4-diaryl-1,3-oxathiolanes; 2,5-diaryl-1,3-oxathiolanes; 2,5-diaryl tetrahydrothiophenes, tetrahydrofurans, and pyrrolidines; 1,3-diaryl cyclopentanes; and 2,4-diaryl tetrahydrothiophenes, tetrahydrofurans and pyrrolidines.

According to the present invention, R^1 groups are added to PAF receptor antagonists at bulk tolerating locations on the molecule. The bulk tolerating areas are easily identified by analysis of the PAF receptor antagonist activity of the compound of interest, and the compound as modified by the addition of chemical moieties at various locations on the molecule. A large amount of information available regarding structure-activity relationships for a variety of PAF receptor antagonists is available and can be used to identify bulk tolerating areas.

The invention is not limited to the modification of specific PAF receptor antagonists, but is instead a general method. Below are provided specific detailed examples of the modification of a number of PAF receptor antagonists. For convenience, Examples 1-7 provide detailed descriptions for methods to convert conventional PAF receptor antagonists into dual function antagonists through the addition of hydroxamate or hydroxyurea moieties to the compounds. It should be understood that these PAF antagonists can also be modified by the addition of oxalkane, thioalkane, quinolylmethoxy, or amidohydroxyurea moieties.

Given these detailed instructions, one of ordinary skill in the art will be able to modify other PAF antagonist molecules in a similar fashion. All modifications of PAF antagonists at bulk tolerating areas with the disclosed 5-lipoxygenase inhibiting moieties are considered within the scope of this invention.

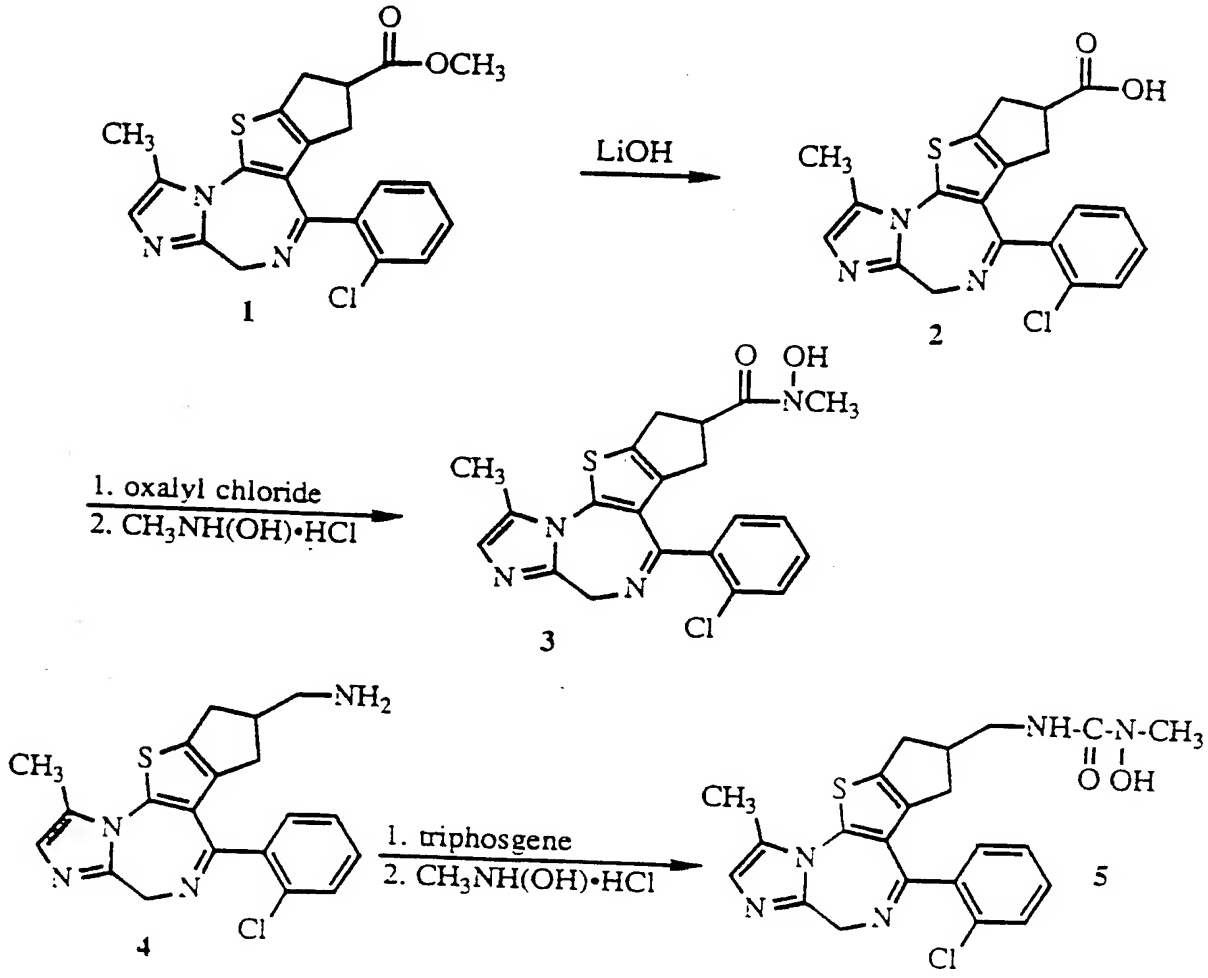
Equivalent or similar reagents and conditions can be substituted for those described below without departing from the scope of the invention.

Example 1: Preparation of Hetrazepines with PAF and 5-Lipoxygenase Inhibiting Activity

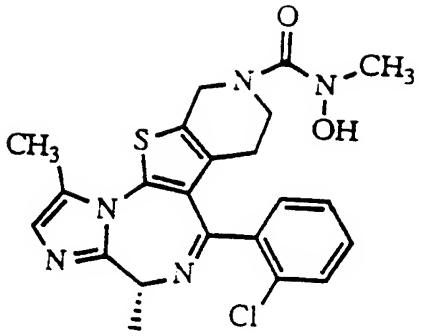
A variety of hetrazepines with PAF receptor antagonist activity are known. Nonlimiting examples of active hetrazepines that can be modified using the disclosed method are disclosed in European Patent Application No. 338 993 A; Ger. Offen. DE 3,936,828; Ger. Offen. DE 4,006,471; Ger. Offen. DE 3,701,344; Ger. Offen. DE 3,724,164; Ger. Offen. DE 3,724,031; US 4,959,361; European Patent Application No. 0 407 955 A1; and European Patent Application No. 0 367 110.

Figure 1 is an illustration of the chemical structures of nonlimiting examples of hetrazepines modified to include hydroxamate and hydroxyurea moieties. Starting from the known thienotriazolodiazepine 1 both hydroxamate and hydroxyurea moieties can be incorporated onto an area of the molecule where a great variety of functionalization has clearly been shown to be tolerated. Thus, as shown in Scheme 1 below, ester 1 is saponified to carboxylic acid 2 with hydroxide. Conversion of

Scheme 1



Scheme 1



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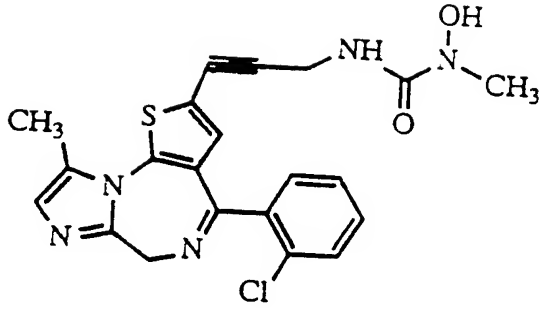

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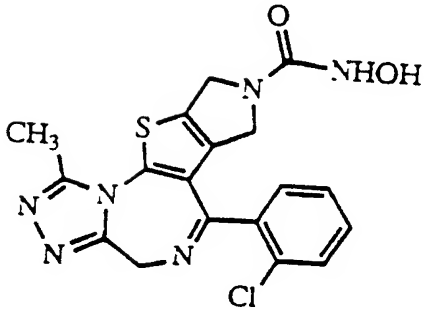

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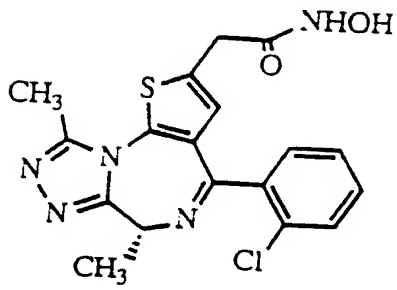


9

acid **2** to the acid chloride followed by addition of methyl hydroxylamine provides the desired hydroxamate **3**. Alternatively, starting from the known thienotriazolodiazepine **4**, the primary amine is converted into a hydroxyurea by sequential reaction with triphosgene and methyl hydroxylamine to furnish **5**. In the same manner, hydroxamates and hydroxyurea containing hetrazepines are synthesized with modified spacer groups between the thiophene ring and the iron chelating moiety. Some additional examples include but are not limited to compounds of types **6-9**.

Specific nonlimiting examples of dual function hetrazepines that can be prepared according to this process are:

Compound 3 (Hydroxamic Acid)
6-(2-chlorophenyl)-3-(N-hydroxy-N-methylamido)-11-methylcyclo-pentyl[1,5:4,5]thieno[3,2-f][1,3]-imidazolo[3,2-a][1,4]-diazepine;

Derivatives of Compound 3:
6-(2-chlorophenyl)-3-(N-ethyl-N-hydroxyamido)-11-methylcyclopen-tyl[1,5:4,5]thieno[3,2-f][1,3]-imidazolo[3,2-a][1,4]-diazepine;

6-(2-chlorophenyl)-3-(N-hydroxy-N-propylamido)-11-methylcyclopen-tyl[1,5:4,5]thieno[3,2-f][1,3]-imidazolo[3,2-a][1,4]-diazepine;

6-(2-chlorophenyl)-3-(N-cyclopropyl-N-hydroxyamido)-11-methylcyclopentyl[1,5:4,5]thieno[3,2-f][1,3]-imidazolo[3,2-a][1,4]-diazepine;

Compound 5 (Hydroxyurea):
6-(2-chlorophenyl)-3-(N-hydroxy-N-methylureidyl-methyl)-11-methyl-cyclopentyl[1,5:4,5]thieno-[3,2-f][1,3]-imidazolo[3,2-a][1,4]-diazepine;

Derivatives of Compound 5:
6-(2-chlorophenyl)-3-(N-ethyl-N-hydroxyureidyl-methyl)-11-methyl-cyclopentyl[1,5:4,5]thieno-[3,2-f][1,3]imidazolo-[3,2-a][1,4]-diazepine;

6-(2-chlorophenyl)-3-(N-hydroxy-N-propylureidyl-methyl)-11-methyl-cyclopentyl[1,5:4,5]thieno-[3,2-f][1,3]imidazolo-[3,2-a][1,4]-diazepine;

6-(2-chlorophenyl)-3-(N-butyl-N-hydroxyureidyl-methyl)-11-methyl-cyclopentyl[1,5:4,5]thieno-[3,2-f][1,3]imidazolo-[3,2-a][1,4]-diazepine;

The Reverse Hydroxyurea of Compound 5:
6-(2-chlorophenyl)-3-(N-hydroxy-N'-methylureidyl-methyl)-11-methylcyclopentyl[1,5:4,5]thieno-[3,2-f][1,3]-imidazolo[3,2-a][1,4]-diazepine;

Derivatives of the Reverse Hydroxyurea of Compound 5
6-(2-chlorophenyl)-3-(N'-benzyl-N-hydroxyureidyl-methyl)-11-methylcyclopentyl[1,5:4,5]thieno[3,2-f]-[1,3]imidazolo-[3,2-a][1,4]-diazepine;

6-(2-chlorophenyl)-3-(N-hydroxy-N'-phenylureidyl-methyl)-11-methylcyclopentyl[1,5:4,5]thieno[3,2-f]-[1,3]imidazolo[3,2-a][1,4]-diazepine;

6-(2-chlorophenyl)-3-(N'-butyl-N-hydroxyureidyl-methyl)-11-methyl-cyclopentyl[1,5:4,5]thieno-[3,2-f][1,3]imidazolo[3,2-a][1,4]-diazepine;

6-(2-chlorophenyl)-3-(N-hydroxyureidylmethyl)-11-methylcyclopentyl[1,5:4,5]thieno[3,2-f][1,3]-imidazolo[3,2-a][1,4]-diazepine;

Hydroxamic acid derivatives of Compound 5:

6-(2-chlorophenyl)-3-(N-acetyl-N-hydroxyamino-methyl)-11-methylcyclopentyl[1,5:4,5]thieno[3,2-f]-[1,3]imidazolo[3,2-a][1,4]-diazepine;

6-(2-chlorophenyl)-3-(N-benzoyl-N-hydroxyamino-methyl)-11-methylcyclopentyl[1,5:4,5]thieno[3,2-f]-[1,3]imidazolo[3,2-a][1,4]-diazepine;

6-(2-chlorophenyl)-3-(N-hydroxy-N-propanoylamino-methyl)-11-methylcyclopentyl[1,5:4,5]thieno[3,2-f]-[1,3]imidazolo[3,2-a][1,4]-diazepine;

6-(2-chlorophenyl)-3-(N-butanoyl-N-hydroxyamino-methyl)-11-methylcyclopentyl[1,5:4,5]thieno[3,2-f]-[1,3]imidazolo[3,2-a][1,4]-diazepine;

Compound 6 (Hydroxyurea):

(8-R)-6-(2-chlorophenyl)-3-(N'-hydroxy-N'-methyl-carboxamido)-8,11-dimethyl-2,3,4,5-tetrahydro-8H-pyridyl[4,3:4,5]thieno[3,2-f][1,3]imidazolo[3,2-a]-[1,4]-diazepine;

Derivatives of Compound 6:

(8-R)-6-(2-chlorophenyl)-3-(N'-ethyl-N'-hydroxy-carboxamido)-8,11-dimethyl-2,3,4,5-tetrahydro-8H-pyridyl[4,3:4,5]thieno[3,2-f][1,3]imidazolo[3,2-a]-[1,4]-diazepine;

(8-R)-6-(2-chlorophenyl)-3-(N'-hydroxy-N'-phenyl-carboxamido)-8,11-dimethyl-2,3,4,5-tetrahydro-8H-pyridyl[4,3:4,5]thieno[3,2-f][1,3]imidazolo[3,2-a]-[1,4]-diazepine;

(8-R)-6-(2-chlorophenyl)-3-(N'-cyclopropyl-N'-hydroxycarboxamido)-8,11-dimethyl-2,3,4,5-tetrahydro-8H-pyridyl[4,3:4,5]thieno[3,2-f][1,3]-imidazolo[3,2-a][1,4]-diazepine;

Compound 8 (Hydroxyurea):
6-(2-chlorophenyl)-3-N-(N'-hydroxycarboxamido)-11-methyl-2,3,4-dihydropyrollo[4,3:4,5]thieno[3,2-f]-[1,2,4]triazolo[4,3-a][1,4]-diazepine;

Derivatives of Compound 8:
6-(2-chlorophenyl)-3-N-(N'-hydroxy-N'-methyl-carboxamido)-11-methyl-2,3,4-dihydropyrollo-[4,3:4,5]thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]-diazepine;

6-(2-chlorophenyl)-3-N-(N'-ethyl-N'-hydroxy-carboxamido)-11-methyl-2,3,4-dihydropyrollo[4,3:4,5]thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]-diazepine;

6-(2-chlorophenyl)-3-N-(N'-hydroxy-N'-phenyl-carboxamido)-11-methyl-2,3,4-dihydropyrollo[4,3:4,5]thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]-diazepine;

6-(2-chlorophenyl)-3-N-(N'-butyl-N'-hydroxy-carboxamido)-11-methyl-2,3,4-dihydropyrollo[4,3:4,5]thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]-diazepine;

Compound 9 (Hydroxamic Acid):
(8-R)-6-(2-chlorophenyl)-5-(N'-hydroxycarboxamido-methyl)-8,11-dimethylthieno[3,2-f][1,2,4]triazolo-[4,3-a][1,4]-diazepine;

Derivatives of Hydroxamic acid 9:
(8-R)-6-(2-chlorophenyl)-5-(N'-hydroxy-N'-methyl-carboxamidomethyl)-8,11-dimethylthieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]-diazepine;

(8-R)-6-(2-chlorophenyl)-5-(N'-p-chlorophenyl-N'-hydroxycarboxamidomethyl)-8,11-dimethylthieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]-diazepine;

(8-R)-6-(2-chlorophenyl)-5-(N'-hydroxy-N'-propyl-carboxamidomethyl)-8,11-dimethylthieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]-diazepine; and

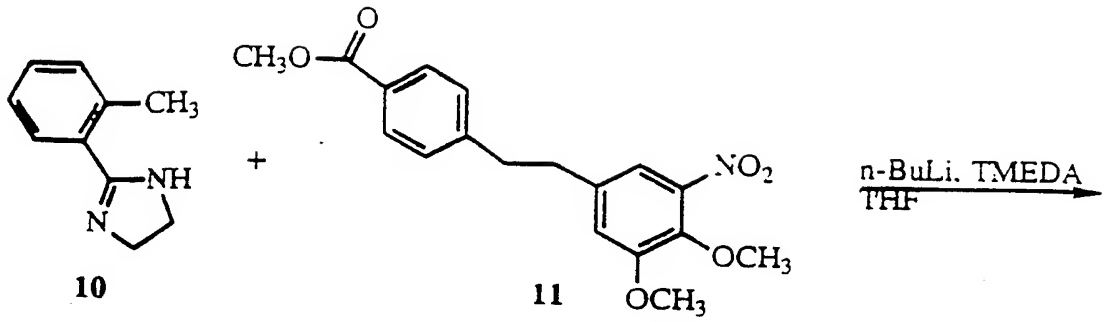
(8-R)-6-(2-chlorophenyl)-5-(N'-butyl-N'-hydroxy-carboxamidomethyl)-8,11-dimethylthieno[3,2-f]-[1,2,4]triazolo[4,3-a][1,4]-diazepine.

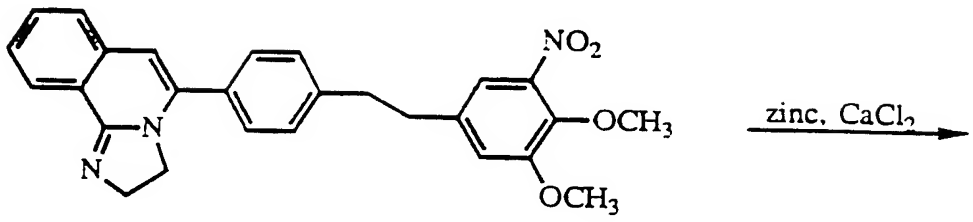
Example 2: Preparation of Dimethoxyphenyl-ethylphenylimidazo[2.1-a]isoquinolines with PAF and 5-Lipoxygenase Inhibiting Activity.

A number of imidazo[2.1-a]isoquinolines with PAF receptor antagonist activity are also known. Nonlimiting examples of imidazo-[2.1-a]isoquinolines PAF receptor antagonists that can be modified according to the present invention to exhibit 5-lipoxygenase inhibiting activity are disclosed in United States Patent Nos. 4,910,206 and 4,992,428.

Figure 2 is an illustration of the chemical structures of nonlimiting examples of imidazo-[2.1-a]isoquinolines modified to include hydroxamate and hydroxyurea moieties. These compounds can be prepared as described in detail in Scheme 2 below.

Scheme 2





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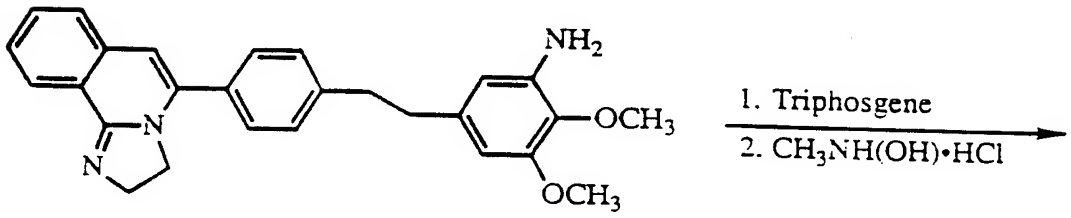

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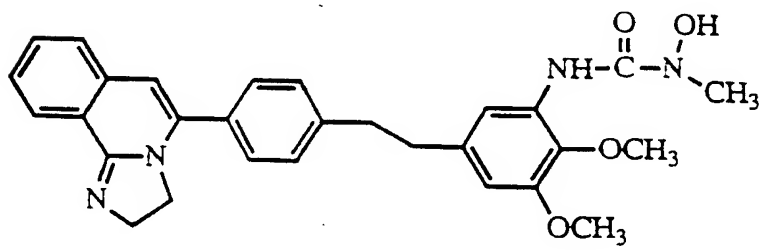

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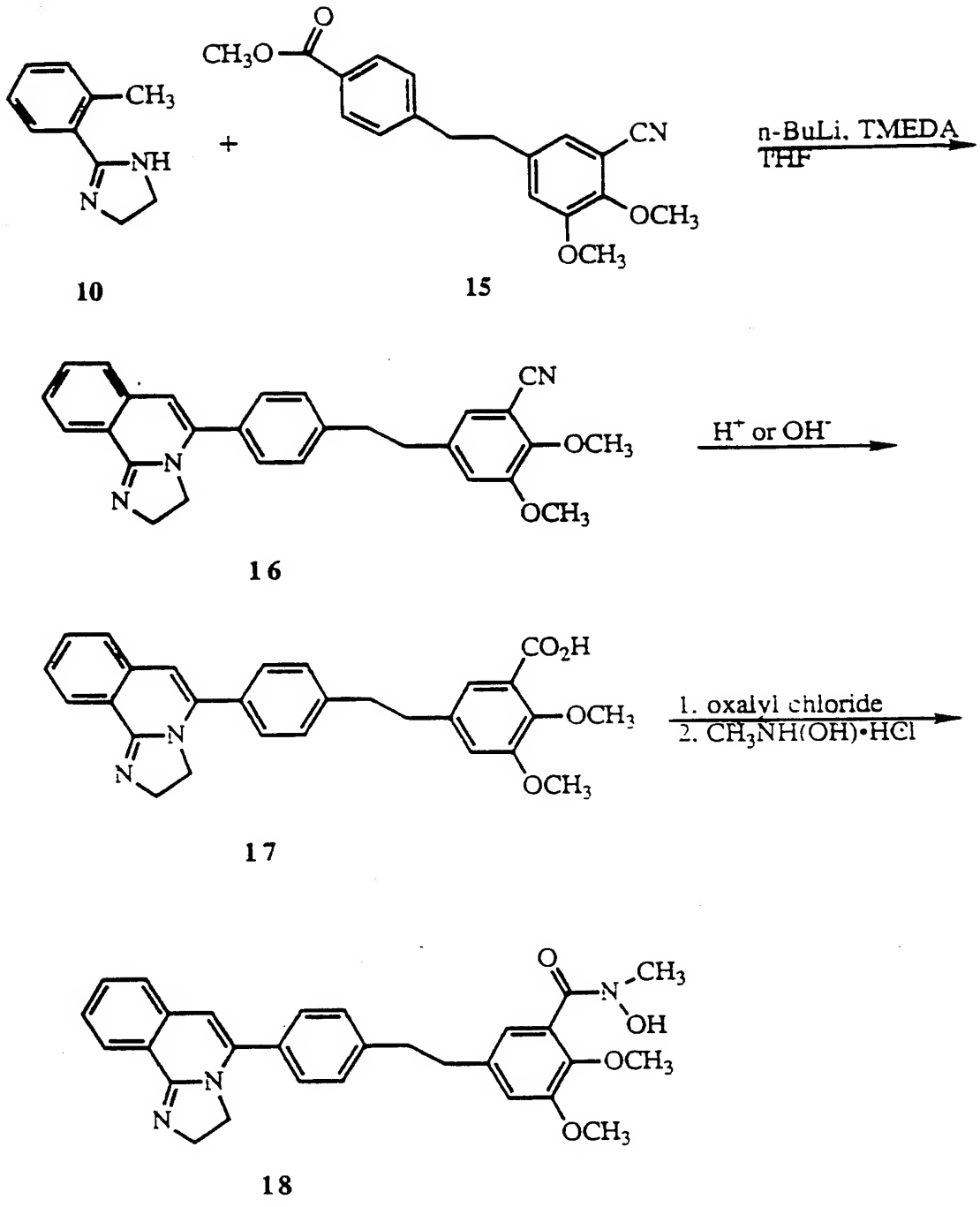
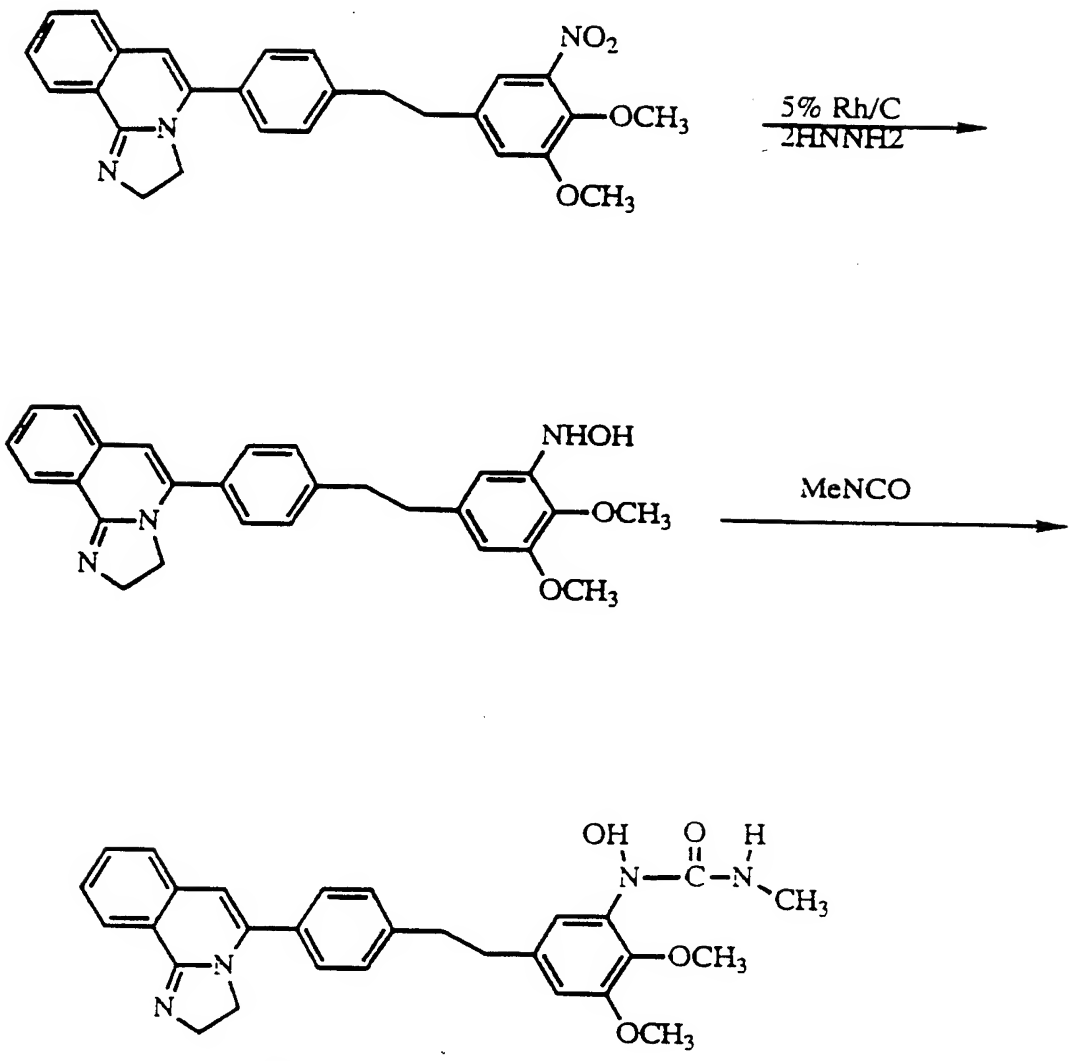
Scheme 2

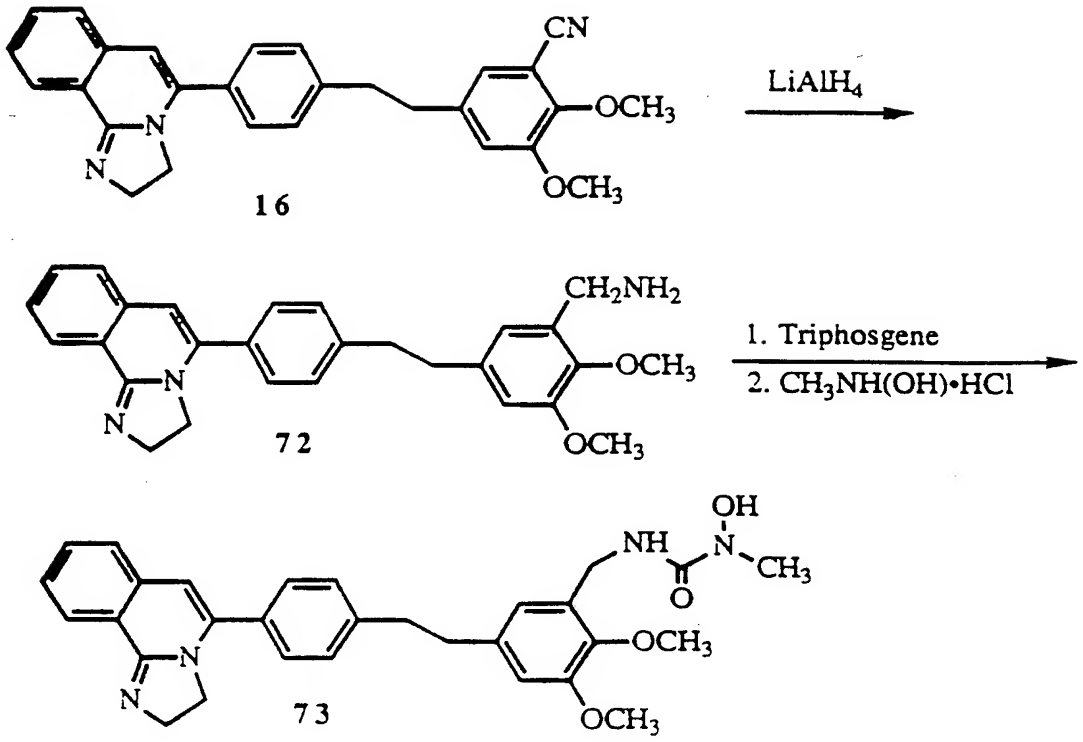

CH3O
O
CH3
NH
N
+
CN
OCH3
OCH3
n-BuLi, TMEDA
THF
10
15
CN
OCH3
OCH3
H+ or OH-
16
CO2H
OCH3
OCH3
1. oxalyl chloride
2. CH3NH(OH)•HCl
17
O
N
CH3
OH
OCH3
OCH3
18

Scheme 2

Reverse Hydroxyurea of **14**



Reverse hydroxyurea of **14**


CN
OCH3
OCH3
LiAlH4
16
CH2NH2
OCH3
OCH3
1. Triphosgene
2. CH3NH(OH)•HCl
72
OH
NH
N
CH3
O
OCH3
OCH3
73

Briefly, the dihydroimidazole **10** is condensed with the nitro ester **11** to give the dihydroimidazo-[1,2-a]isoquinoline **12**. Reduction of the nitro group to the amine with zinc metal yields the amino heterocycle **13** which is treated first with triphosgene and then with a hydroxylamine (methyl hydroxylamine was used in this example but any substitution is possible) to give the hydroxyurea **14**.

In a similar fashion the hydroxamic acid can be prepared starting from the dihydroimidazole **10** and the cyano ester **15**. The resultant dihydroimidazoquinoline can then be hydrolyzed to the acid **17** which is converted via its acid chloride to the hydroxamic acid **18**.

The reverse hydroxyurea of compound **14** can be prepared by reduction of the nitro ester **12** to the corresponding hydroxylamine, that is reacted with CH_3NCO to provide the product hydroxyurea.

Nonlimiting examples of dual function imidazo[2.1-a]isoquinolines that can be prepared according to this process are:

Compound 14 (Hydroxyurea):
5-[4'-(3-(N-hydroxy-N-methylureidyl)-4,5-dimethoxyphenylethyl)phenyl]-2,3-dihydroimidazo[2,1-a]-isoquinoline;

Derivatives of Compound 14:
5-[4'-(3-(N-hydroxyureidyl)-4,5-dimethoxyphenylethyl)phenyl]-2,3-dihydro-imidazo[2,1-a]-isoquinoline;

5-[4'-(3-(N-ethyl-N-hydroxyureidyl)-4,5-dimethoxyphenylethyl)phenyl]-2,3-dihydroimidazo[2,1-a]-isoquinoline;

5-[4'-(3-(N-hydroxy-N-propylureidyl)-4,5-dimethoxyphenylethyl)phenyl]-2,3-dihydroimidazo[2,1-a]-isoquinoline;

5-[4'-(3-(N-cyclopropyl-N-hydroxyureidyl)-4,5-dimethoxyphenylethyl)phenyl]-2,3-dihydroimidazo-[2,1-a]isoquinoline;

Reverse Hydroxyurea of Compound 14:
5-[4'-(3-(N'-methyl-N-hydroxyureidyl)-4,5-dimethoxyphenylethyl)phenyl]-2,3-dihydro-imidazo[2,1-a]-isoquinoline;

Derivatives of Reverse hydroxyurea 14:
5-[4'-(3-(N-hydroxyureidyl)-4,5-dimethoxyphenylethyl)phenyl]-2,3-dihydro-imidazo[2,1-a]-isoquinoline;

5-[4'-(3-(N'-ethyl-N-hydroxyureidyl)-4,5-dimethoxyphenylethyl)phenyl]-2,3-dihydroimidazo[2,1-a]-isoquinoline;

5-[4'-(3-(N-hydroxy-N'-phenylureidyl)-4,5-dimethoxyphenylethyl)phenyl]-2,3-dihydroimidazo[2,1-a]-isoquinoline;

5-[4'-(3-(N'-butyl-N-hydroxyureidyl)-4,5-dimethoxyphenylethyl)phenyl]-2,3-dihydroimidazo[2,1-a]-isoquinoline;

Compound 18 (Hydroxamic Acid):
5-[4'-(3-(N-methyl-N-hydroxycarboxamido)-4,5-dimethoxyphenylethyl)phenyl]-2,3-dihydroimidazo-[2,1-a]isoquinoline;

Derivatives of Hydroxamic acid 18:
5-[4'-(3-(N-hydroxycarboxamido)-4,5-dimethoxy-phenyl-ethyl)-phenyl]-2,3-dihydro-imidazo[2,1-a]-isoquinoline;

5-[4'-(3-(N-ethyl-N-hydroxycarboxamido)-4,5-dimethoxyphenylethyl)phenyl]-2,3-dihydroimidazo-[2,1-a]isoquinoline;

5-[4'-(3-(N-propyl-N-hydroxycarboxamido)-4,5-dimethoxyphenylethyl)phenyl]-2,3-dihydroimidazo-[2,1-a]isoquinoline; and

5-[4'-(3-(N-butyl-N-hydroxycarboxamido)-4,5-dimethoxyphenylethyl)phenyl]-2,3-dihydroimidazo-[2,1-a]isoquinoline;

Example 3: Preparation of Pyrrolo[1,2-c]thiazole with PAF and 5-Lipoxygenase Inhibiting Activity

Pyrrolo[1,2-c]thiazoles with PAF receptor antagonist activity can also be modified using the disclosed process to impart 5-lipoxygenase inhibiting activity to the molecules. Nonlimiting examples of pyrrolo[1,2-c]thiazoles that can be converted into dual function antagonists are described, for example, in Lave et al., Drugs of the Future, 14(9), 891 (1989); European Patent Application No. 388 309 A2; and European Patent Application No. 0 252 823 A1.

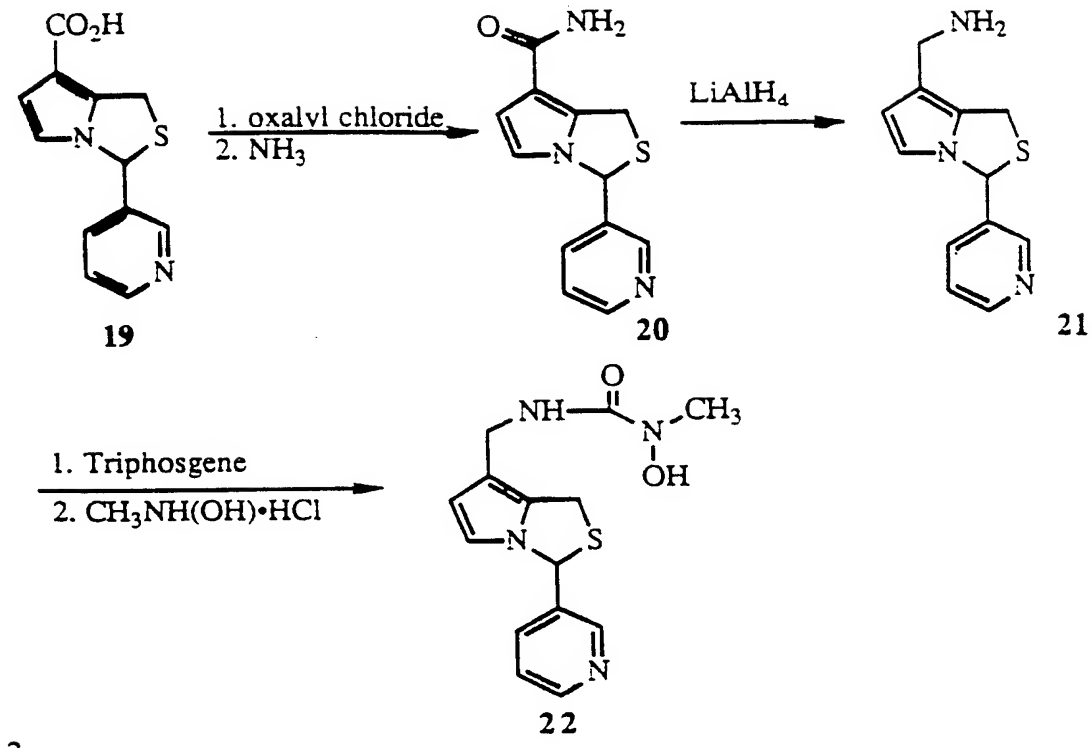
Figure 3 is an illustration of nonlimiting examples of pyrrolo[1,2-c]thiazoles modified through the addition of hydroxamate or hydroxyurea groups to impart 5-lipoxygenase inhibiting activity to the compound. These compounds can be synthesized as illustrated in Scheme 3 below, using pyrrolo[1,2-c]thiazole carboxylic acid **19** as the starting material. The carboxylic acid **19** is

converted to the amide **20** by treatment with oxalyl chloride followed by ammonia. Reduction of the amide with lithium aluminum hydride provides the amine **21**. Treatment of the amine **21** with triphosgene followed by methyl hydroxylamine hydrochloride gives the hydroxyurea **22**. In a second pathway, treatment of the carboxylic acid **19** with oxalyl chloride followed by a nitroaniline gives the amide **23**. Reduction of the nitro group with sodium dithionite then yields the aniline **24**. Treatment with triphosgene and then with a hydroxylamine such as methyl hydroxylamine hydrochloride then yields the hydroxyurea **25**.

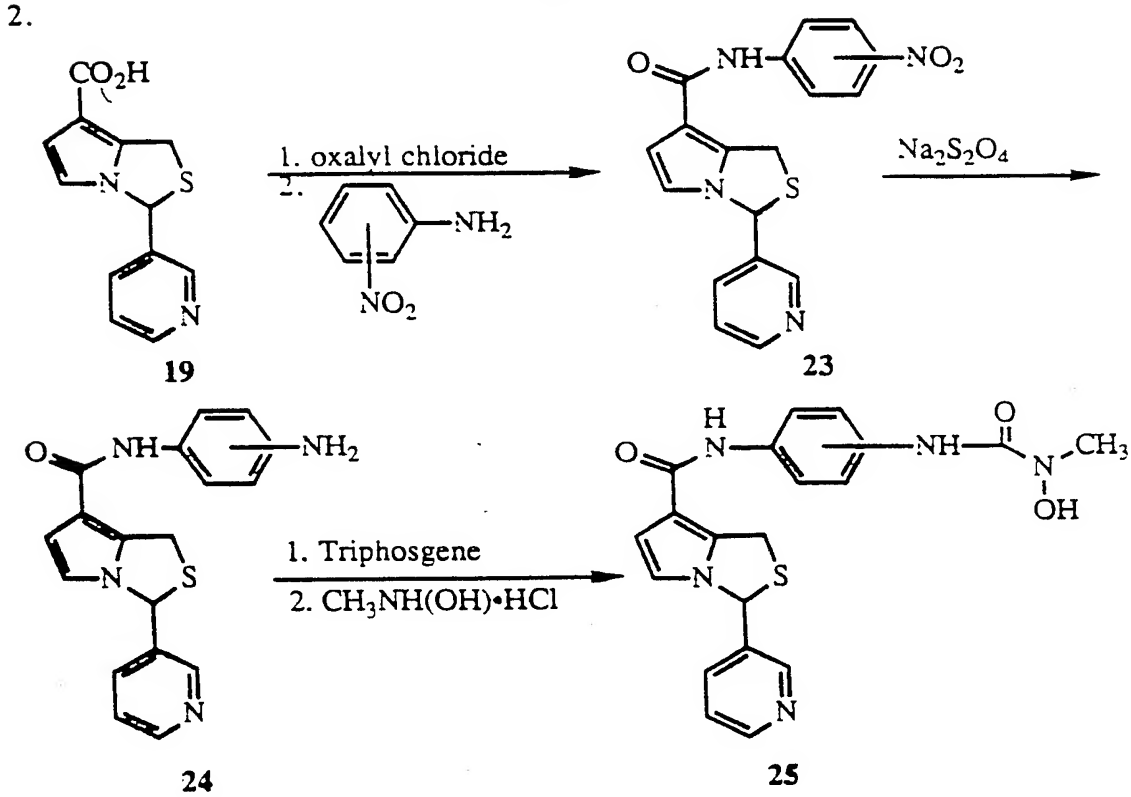
According to pathway three of Scheme 3, pyrrolo[1,2-c]carboxylic acid **19** is treated with oxalyl chloride followed by a hydroxylamine to provide the pyrrolo[1,2-c]thiazole hydroxamic acid **26**.

Scheme 3

1.

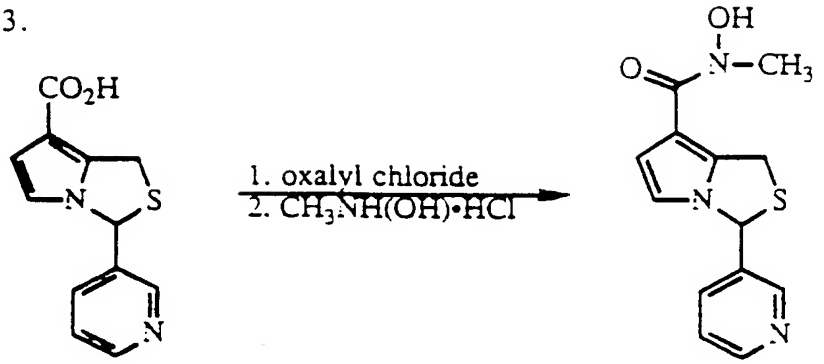

CO2H
1. oxalyl chloride
2. NH3
NH2
LiAlH4
NH2
19
20
21
1. Triphosgene
2. CH3NH(OH)•HCl
NH
CH3
OH
22

2.


CO2H
1. oxalyl chloride
2.
NH2
NO2
NH
NO2
Na2S2O4
19
23
NH
NH2
1. Triphosgene
2. CH3NH(OH)•HCl
H
N
NH
CH3
OH
24
25

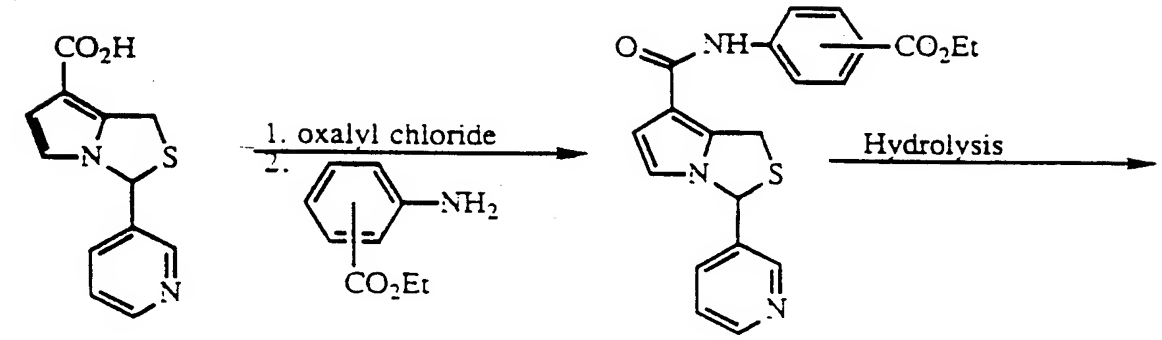
Scheme 3

3.

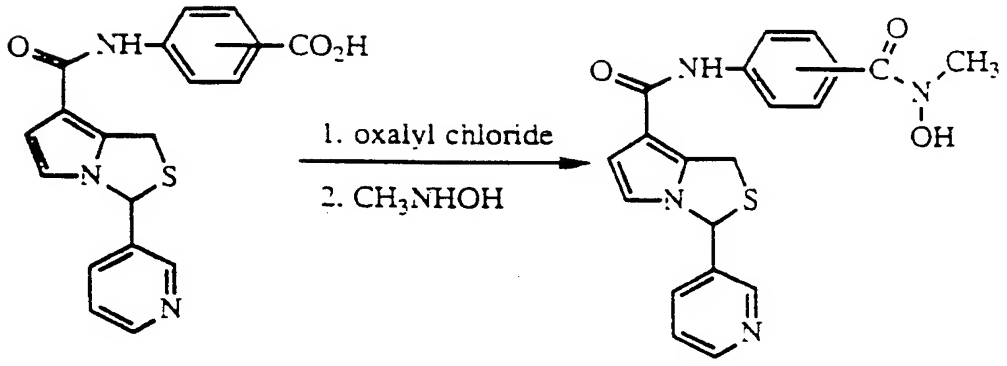


19 26

4.



19 27



28 29

The preparation of hydroxyurea amides is illustrated in pathway 4 of Scheme 3. In this case the pyrrolo[1,2-c]thiazole carboxylic acid **19** is treated with oxalyl chloride and a carbethoxyaniline to produce the amide **27**. Hydrolysis of the ester in compound **27** yields the acid **28** which is then converted to the hydroxamic acid **29**.

Specific nonlimiting examples of dual function pyrrolo[1,2-c]thiazoles that can be prepared according to this process are:

Compound 22 (Hydroxyurea):
7-(N-hydroxy-N-methylureidylmethyl)-3-(3-pyridyl)-1H,3H-pyrrolo[1,2-c]thiazole;

Derivatives of Hydroxyurea 22:
7-(N-hydroxyureidylmethyl)-3-(3-pyridyl)-1H,3H-pyrrolo[1,2-c]thiazole;

7-(N-ethyl-N-hydroxyureidylmethyl)-3-(3-pyridyl)-1H,3H-pyrrolo[1,2-c]thiazole;

7-(N-hydroxy-N-phenylureidylmethyl)-3-(3-pyridyl)-1H,3H-pyrrolo[1,2-c]thiazole;

7-(N-cyclopropyl-N-hydroxyureidylmethyl)-3-(3-pyridyl)-1H,3H-pyrrolo[1,2-c]thiazole;

Reverse Hydroxyurea of Compound 22:
7-(N-hydroxy-N'-methylureidylmethyl)-3-(3-pyridyl)-1H,3H-pyrrolo[1,2-c]thiazole;

Derivatives of Reverse Hydroxyurea of Compound 22:
7-(N-hydroxyureidylmethyl)-3-(3-pyridyl)-1H,3H-pyrrolo[1,2-c]thiazole;

7-(N'-benzyl-N-hydroxyureidylmethyl)-3-(3-pyridyl)-1H,3H-pyrrolo[1,2-c]thiazole;

7-(N-hydroxy-N'-propylureidylmethyl)-3-(3-pyridyl)-1H,3H-pyrrolo[1,2-c]thiazole;

7-(N'-butyl-N-hydroxyureidylmethyl)-3-(3-pyridyl)-1H,3H-pyrrolo[1,2-c]thiazole;

Compound 25 (Hydroxyurea):
N-(4-(N-hydroxy-N-methylureidylphenyl)-3-(3-pyridyl)-1H,3H-pyrrolo[1,2-c]thiazole-7-carboxamide;

Derivatives of Hydroxyurea 25:
N-(4-(N-hydroxyureidylphenyl)-3-(3-pyridyl)-1H,3H-pyrrolo[1,2-c]thiazole-7-carboxamide;

N-(4-(N-ethyl-N-hydroxyureidylphenyl)-3-(3-pyridyl)-1H,3H-pyrrolo[1,2-c]thiazole-7-carboxamide;

N-(4-(N-hydroxy-N-phenylureidylphenyl)-3-(3-pyridyl)-1H,3H-pyrrolo[1,2-c]thiazole-7-carboxamide;

N-(4-(N-butyl-N-hydroxyureidylphenyl)-3-(3-pyridyl)-1H,3H-pyrrolo[1,2-c]thiazole-7-carboxamide;

N-(3-(N-hydroxyureidylphenyl)-3-(3-pyridyl)-1H,3H-pyrrolo[1,2-c]thiazole-7-carboxamide;

N-(3-(N-hydroxy-N-methylureidylphenyl)-3-(3-pyridyl)-1H,3H-pyrrolo[1,2-c]thiazole-7-carboxamide;

N-(3-(N-ethyl-N-hydroxyureidylphenyl)-3-(3-pyridyl)-1H,3H-pyrrolo[1,2-c]thiazole-7-carboxamide;

N-(3-(N-hydroxy-N-propylureidylphenyl)-3-(3-pyridyl)-1H,3H-pyrrolo[1,2-c]thiazole-7-carboxamide;

N-(3-(N-cyclopropyl-N-hydroxyureidylphenyl)-3-(3-pyridyl)-1H,3H-pyrrolo[1,2-c]thiazole-7-carboxamide;

N-(2-(N-hydroxyureidylphenyl)-3-(3-pyridyl)-1H,3H-pyrrolo[1,2-c]thiazole-7-carboxamide;

N-(2-(N-hydroxy-N-methylureidylphenyl)-3-(3-pyridyl)-1H,3H-pyrrolo[1,2-c]thiazole-7-carboxamide;

N-(2-(N-ethyl-N-hydroxyureidylphenyl)-3-(3-pyridyl)-1H,3H-pyrrolo[1,2-c]thiazole-7-carboxamide;

N-(2-(N-hydroxy-N-phenylureidylphenyl)-3-(3-pyridyl)-1H,3H-pyrrolo[1,2-c]thiazole-7-carboxamide;

N-(2-(N-butyl-N-hydroxyureidylphenyl)-3-(3-pyridyl)-1H,3H-pyrrolo[1,2-c]thiazole-7-carboxamide;

Reverse Hydroxyurea 25:

N-(4-(N-hydroxy-N'-methylureidylphenyl)-3-(3-pyridyl)-1H,3H-pyrrolo[1,2-c]thiazole-7-carboxamide;

Derivatives of hydroxyurea 25:

N-(4-(N-hydroxyureidylphenyl)-3-(3-pyridyl)-1H,3H-pyrrolo[1,2-c]thiazole-7-carboxamide;

N-(4-(N'-ethyl-N-hydroxyureidylphenyl)-3-(3-pyridyl)-1H,3H-pyrrolo[1,2-c]thiazole-7-carboxamide;

N-(4-(N-hydroxy-N'-propylureidylphenyl)-3-(3-pyridyl)-1H,3H-pyrrolo[1,2-c]thiazole-7-carboxamide;

N-(4-(N'-butyl-N-hydroxyureidylphenyl)-3-(3-pyridyl)-1H,3H-pyrrolo[1,2-c]thiazole-7-carboxamide;

N-(3-(N-hydroxyureidylphenyl)-3-(3-pyridyl)-1H,3H-pyrrolo[1,2-c]thiazole-7-carboxamide;

N-(3-(N-hydroxy-N'-methylureidylphenyl)-3-(3-pyridyl)-1H,3H-pyrrolo[1,2-c]thiazole-7-carboxamide;

N-(3-(N'-benzyl-N-hydroxyureidylphenyl)-3-(3-pyridyl)-1H,3H-pyrrolo[1,2-c]thiazole-7-carboxamide;

N-(3-(N'-cyclopropyl-N-hydroxyureidylphenyl)-3-(3-pyridyl)-1H,3H-pyrrolo[1,2-c]thiazole-7-carboxamide;

N-(3-(N'-butyl-N-hydroxyureidylphenyl)-3-(3-pyridyl)-1H,3H-pyrrolo[1,2-c]thiazole-7-carboxamide;

N-(2-(N-hydroxyureidylphenyl)-3-(3-pyridyl)-1H,3H-pyrrolo[1,2-c]thiazole-7-carboxamide;

N-(2-(N'-ethyl-N-hydroxyureidylphenyl)-3-(3-pyridyl)-1H,3H-pyrrolo[1,2-c]thiazole-7-carboxamide;

N-(2-(N-hydroxy-N'-phenylureidylphenyl)-3-(3-pyridyl)-1H,3H-pyrrolo[1,2-c]thiazole-7-carboxamide;

N-(2-(N'-cyclopropyl-N-hydroxyureidylphenyl)-3-(3-pyridyl)-1H,3H-pyrrolo[1,2-c]thiazole-7-carboxamide;

N-(2-(N'-butyl-N-hydroxyureidylphenyl)-3-(3-pyridyl)-1H,3H-pyrrolo[1,2-c]thiazole-7-carboxamide;

Hydroxamic acid 26:
3-(3-pyridyl)-1H,3H-pyrrolo[1,2-c]thiazole-7-N-hydroxy-N-methylcarboxamide;

Derivatives of hydroxamic acid 26:
3-(3-pyridyl)-1H,3H-pyrrolo[1,2-c]thiazole-7-N-ethyl-N-hydroxycarboxamide;

3-(3-pyridyl)-1H,3H-pyrrolo[1,2-c]thiazole-7-N-hydroxy-N-propylcarboxamide;

3-(3-pyridyl)-1H,3H-pyrrolo[1,2-c]thiazole-7-N-butyl-N-hydroxycarboxamide;

Hydroxamic acid 29:
N-(4-(N-hydroxy-N-methylcarboxamidophenyl)-3-(3-pyridyl)-1H,3H-pyrrolo[1,2-c]thiazole-7-carboxamide;

Derivatives of hydroxyurea 29:
N-(4-(N-hydroxycarboxamidophenyl)-3-(3-pyridyl)-1H, 3H-pyrrolo[1,2-c]thiazole-7-carboxamide;

N-(4-(N-ethyl-N-hydroxycarboxamidophenyl)-3-(3-pyridyl)-1H,3H-pyrrolo[1,2-c]thiazole-7-carboxamide;

N-(4-(N-hydroxy-N-phenylcarboxamidophenyl)-3-(3-pyridyl)-1H,3H-pyrrolo[1,2-c]thiazole-7-carboxamide;

N-(4-(N-cyclopropyl-N-hydroxycarboxamidophenyl)-3-(3-pyridyl)-1H,3H-pyrrolo[1,2-c]thiazole-7-carboxamide;

N-(3-(N-hydroxycarboxamidophenyl)-3-(3-pyridyl)-1H, 3H-pyrrolo[1,2-c]thiazole-7-carboxamide;

N-(3-(N-hydroxy-N-methylcarboxamidophenyl)-3-(3-pyridyl)-1H,3H-pyrrolo[1,2-c]thiazole-7-carboxamide;

N-(3-(N-ethyl-N-hydroxycarboxamidophenyl)-3-(3-pyridyl)-1H,3H-pyrrolo[1,2-c]thiazole-7-carboxamide;

N-(3-(N-hydroxy-N-propylcarboxamidophenyl)-3-(3-pyridyl)-1H,3H-pyrrolo[1,2-c]thiazole-7-carboxamide;

N-(3-(N-butyl-N-hydroxycarboxamidophenyl)-3-(3-pyridyl)-1H,3H-pyrrolo[1,2-c]thiazole-7-carboxamide;

N-(2-(N-hydroxycarboxamidophenyl)-3-(3-pyridyl)-1H, 3H-pyrrolo[1,2-c]thiazole-7-carboxamide;

N-(2-(N-hydroxy-N-methylcarboxamidophenyl)-3-(3-pyridyl)-1H,3H-pyrrolo[1,2-c]thiazole-7-carboxamide;

N-(2-(N-ethyl-N-hydroxycarboxamidophenyl)-3-(3-pyridyl)-1H,3H-pyrrolo[1,2-c]thiazole-7-carboxamide;

N-(2-(N-hydroxy-N-phenylcarboxamidophenyl)-3-(3-pyridyl)-1H,3H-pyrrolo[1,2-c]thiazole-7-carboxamide; and

N-(2-(N-butyl-N-hydroxycarboxamidophenyl)-3-(3-pyridyl)-1H,3H-pyrrolo[1,2-c]thiazole-7-carboxamide.

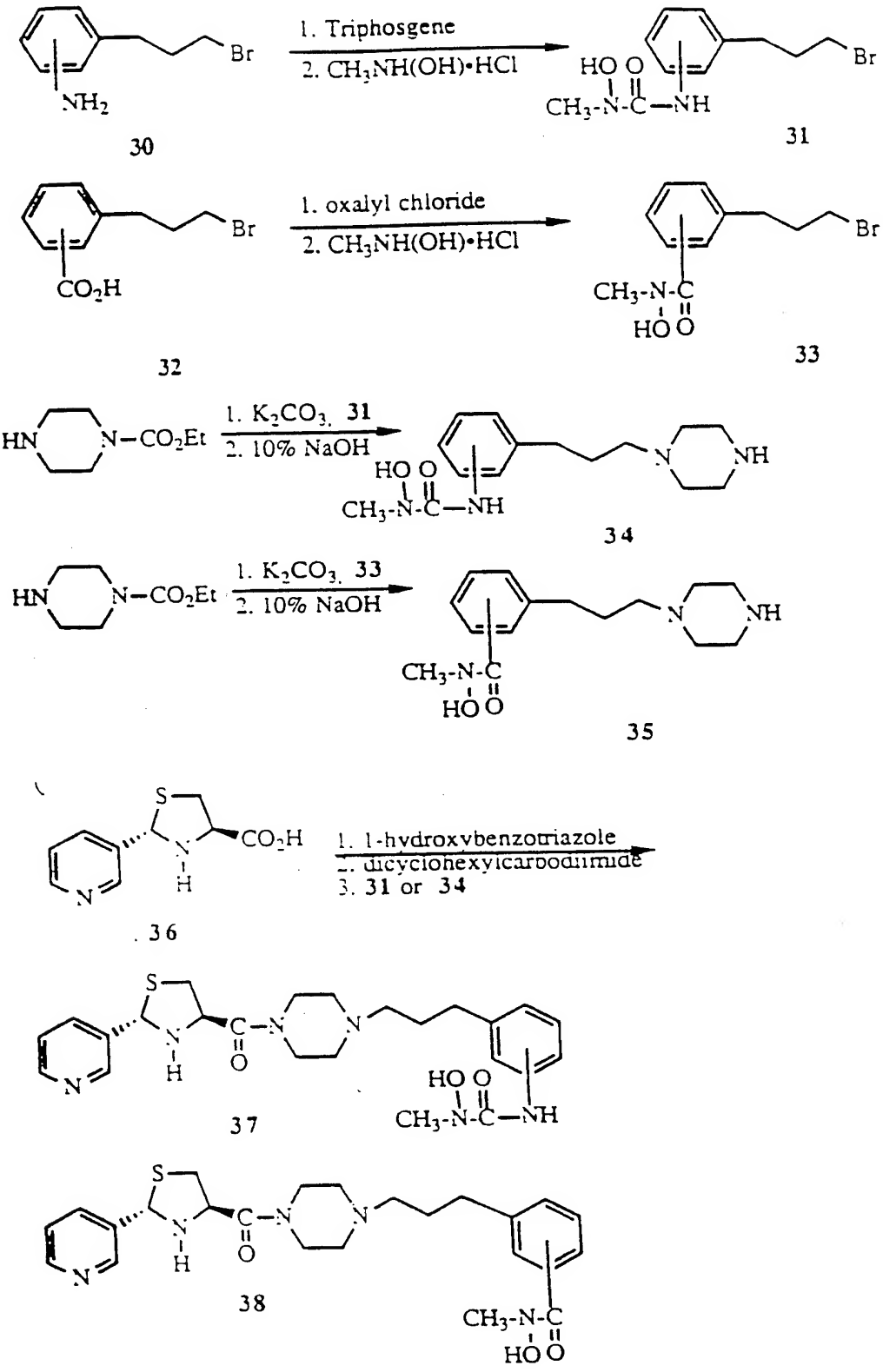
Example 4: Preparation of Thiazolidine-carboxamides with PAF and 5-Lipoxygenase Inhibiting Activity

Nonlimiting examples of thiazolidine-carboxamides with PAF receptor antagonist activity that can be modified to exhibit 5-lipoxygenase inhibiting activity are disclosed in U.S. Patent No. 4,987,132. Illustrative examples of thiazolidinecarboxamides modified to have 5-lipoxygenase inhibiting activity are illustrated in Figure 4. These compounds can be prepared as exemplified in Scheme 4 below. The alkyl amine **30** is treated with triphosgene and methyl hydroxylamine to provide the hydroxyurea **31**. Reaction of the hydroxyurea with carbethoxypiperazine under basic conditions gives the alkyl piperazine **34**. Esterification of thiazolidine **36** with the piperazine **34** gives the dual function antagonist **37**.

The preparation of the hydroxamic acid dual function antagonist **38** starts with the carboxylic acid **32** which is converted to the acid chloride and

treated with methyl hydroxylamine to provide the hydroxamic acid **33**. Treatment of **33** with carbethoxypiperazine under basic conditions yields the alkyl piperazine **35**. Esterification of the thiazolidine carboxylic acid **36** with the piperazine **35** yields the dual function antagonist **38**.

Scheme 4



30 31 32 33 34 35 36 37 38

Nonlimiting examples of dual function thiazolidinecarboxamides that can be prepared according to this process are:

Compound 37 (Hydroxyurea):

1-(3-(4'-N-hydroxy-N-methylureidylphenyl)propyl)-4-[2-(3-pyridyl)thiazolidine-4-yl-carbonyl] piperazine;

Derivatives of Hydroxyurea 37:

1-(3-(4'-N-hydroxylureidylphenyl)propyl)-4-[2-(3-pyridyl)-thiazolidine-4-yl-carbonyl]piperazine;

1-(3-(4'-N-ethyl-N-hydroxyureidylphenyl)phenyl)-4-[2-(3-pyridyl)thiazolidine-4-yl-carbonyl]-piperazine;

1-(3-(4'-N-hydroxy-N-propylureidylphenyl)propyl)-4-[2-(3-pyridyl)thiazolidine-4-yl-carbonyl]-piperazine;

1-(3-(4'-N-cyclopropyl-N-hydroxyureidylphenyl)-propyl)-4-[2-(3-pyridyl)thiazolidine-4-yl-carbonyl]piperazine;

1-(3-(3'-N-hydroxyureidylphenyl)propyl)-4-[2-(3-pyridyl)-thiazolidine-4-yl-carbonyl]piperazine;

1-(3-(3'-N-hydroxy-N-methylureidylphenyl)propyl)-4-[2-(3-pyridyl)thiazolidine-4-yl-carbonyl] piperazine;

1-(3-(3'-N-ethyl-N-hydroxyureidylphenyl)propyl)-4-[2-(3-pyridyl)thiazolidine-4-yl-carbonyl] piperazine;

1-(3-(3'-N-hydroxy-N-phenylureidylphenyl)propyl)-4-[2-(3-pyridyl)thiazolidine-4-yl-carbonyl]-piperazine;

1-(3-(3'-N-butyl-N-hydroxyureidylphenyl)propyl)-4-[2-(3-pyridyl)thiazolidine-4-yl-carbonyl]-piperazine;

1-(3-(2'-N-hydroxyureidylphenyl)propyl)-4-[2-(3-pyridyl)thiazolidine-4-yl-carbonyl]piperazine;

1-(3-(2'-N-hydroxy-N-methylureidylphenyl)propyl)-4-[2-(3-pyridyl)thiazolidine-4-yl-carbonyl]-piperazine;

1-(3-(2'-N-ethyl-N-hydroxyureidylphenyl)propyl)-4-[2-(3-pyridyl)thiazolidine-4-yl-carbonyl]-piperazine;

1-(3-(2'-N-hydroxy-N-phenylureidylphenyl)propyl)-4-[2-(3-pyridyl)thiazolidine-4-yl-carbonyl]-piperazine; and

1-(3-(2'-N-butyl-N-hydroxyureidylphenyl)propyl)-4-[2-(3-pyridyl)thiazolidine-4-yl-carbonyl]-piperazine.

Reverse Hydroxyurea of Compound 37:
1-(3-(4'-N'-ethyl-N-hydroxyureidylphenyl)propyl)-4-[2-(3-pyridyl)thiazolidine-4-yl-carbonyl]-piperazine;

Derivatives of Reverse Hydroxyurea 37:
1-(3-(4'-N-hydroxyureidylphenyl)propyl)-4-[2-(3-pyridyl)-thiazolidine-4-yl-carbonyl]piperazine;

1-(3-(4'-N'-benzyl-N-hydroxyureidylphenyl)propyl)-4-[2-(3-pyridyl)thiazolidine-4-yl-carbonyl]-piperazine;

1-(3-(4'-N-hydroxy-N'-propylureidylphenyl)propyl)-4-[2-(3-pyridyl)thiazolidine-4-yl-carbonyl]-piperazine;

1-(3-(4'-N'-cyclopropyl-N-hydroxyureidylphenyl)-propyl)-4-[2-(3-pyridyl)thiazolidine-4-yl-carbonyl]piperazine;

1-(3-(3'-N-hydroxyureidylphenyl)propyl)-4-[2-(3-pyridyl)-thiazolidine-4-yl-carbonyl]piperazine;

1-(3-(3'-N-hydroxy-N'-methylureidylphenyl)propyl)-4-[2-(3-pyridyl)thiazolidine-4-yl-carbonyl] piperazine;

1-(3-(3'-N'-ethyl-N-hydroxyureidylphenyl)propyl)-4-[2-(3-pyridyl)thiazolidine-4-yl-carbonyl]-piperazine;

1-(3-(3'-N'-cyclopropyl-N-hydroxyureidylphenyl)-propyl)-4-[2-(3-pyridyl)thiazolidine-4-yl-carbonyl]piperazine;

1-(3-(3'-N'-p-chlorophenyl-N-hydroxyureidylphenyl)-propyl)-4-[2-(3-pyridyl)thiazolidine-4-yl-carbonyl]piperazine;

1-(3-(2'-N-hydroxyureidylphenyl)propyl)-4-[2-(3-pyridyl)-thiazolidine-4-yl-carbonyl]piperazine;

1-(3-(2'-N-hydroxy-N'-methylureidylphenyl)propyl)-4-[2-(3-pyridyl)thiazolidine-4-yl-carbonyl]-piperazine;

1-(3-(2'-N'-ethyl-N-hydroxyureidylphenyl)propyl)-4-[2-(3-pyridyl)thiazolidine-4-yl-carbonyl]-piperazine;

1-(3-(2'-N-hydroxy-N'-phenylureidylphenyl)propyl)-4-[2-(3-pyridyl)thiazolidine-4-yl-carbonyl]-piperazine;

1-(3-(2'-N'-butyl-N-hydroxyureidylphenyl)propyl)-4-[2-(3-pyridyl)thiazolidine-4-yl-carbonyl]-piperazine;

Compound 38 (Hydroxamic Acid):
1-(3-(4'-N-hydroxy-N-methylcarboxamidophenyl)-propyl)-4-[2-(3-pyridyl)thiazolidine-4-yl-carbonyl]piperazine;

Derivatives of Hydroxamic acid 38:
1-(3-(4'-N-hydroxycarboxamidophenyl)propyl)-4-[2-(3-pyridyl)thiazolidine-4-yl-carbonyl]piperazine;

1-(3-(4'-N-ethyl-N-hydroxycarboxamidophenyl)-propyl)-4-[2-(3-pyridyl)thiazolidine-4-yl-carbonyl]piperazine;

1-(3-(4'-N-hydroxy-N-propylcarboxamidophenyl)-propyl)-4-[2-(3-pyridyl)thiazolidine-4-yl-carbonyl]piperazine;

1-(3-(4'-N-cyclopropyl-N-hydroxycarboxamidophenyl)-propyl)-4-[2-(3-pyridyl)thiazolidine-4-yl-carbonyl]piperazine;

1-(3-(3'-N-hydroxycarboxamidophenyl)propyl)-4-[2-(3-pyridyl)thiazolidine-4-yl-carbonyl]piperazine;

1-(3-(3'-N-hydroxy-N-methylcarboxamidophenyl)-propyl)-4-[2-(3-pyridyl)thiazolidine-4-yl-carbonyl]piperazine;

1-(3-(3'-N-ethyl-N-hydroxycarboxamidophenyl)-propyl)-4-[2-(3-pyridyl)thiazolidine-4-yl-carbonyl]piperazine;

1-(3-(3'-N-hydroxy-N-phenylcarboxamidophenyl)-propyl)-4-[2-(3-pyridyl)thiazolidine-4-yl-carbonyl]piperazine;

1-(3-(3'-N-butyl-N-hydroxycarboxamidophenyl)-propyl)-4-[2-(3-pyridyl)thiazolidine-4-yl-carbonyl]piperazine;

1-(3-(2'-N-hydroxycarboxamidophenyl)propyl)-4-[2-(3-pyridyl)thiazolidine-4-yl-carbonyl]piperazine;

1-(3-(2'-N-hydroxy-N-methylcarboxamidophenyl)-propyl)-4-[2-(3-pyridyl)thiazolidine-4-yl-carbonyl]piperazine;

1-(3-(2'-N-ethyl-N-hydroxycarboxamidophenyl)-propyl)-4-[2-(3-pyridyl)thiazolidine-4-yl-carbonyl]piperazine;

1-(3-(2'-N-hydroxy-N-propylcarboxamidophenyl)-propyl)-4-[2-(3-pyridyl)thiazolidine-4-yl-carbonyl]piperazine;

1-(3-(2'-N-butyl-N-hydroxycarboxamidophenyl)-propyl)-4-[2-(3-pyridyl)thiazolidine-4-yl-carbonyl]piperazine;

Reverse Hydroxamic Acid of Compound 38:
1-(3-(4'-N-acetyl-N-hydroxyaminophenyl)propyl)-4-[2-(3-pyridyl)thiazolidine-4-yl-carbonyl]-piperazine;

Derivatives of hydroxamic acid 38:
1-(3-(4'-N-ethanoyl-N-hydroxyaminophenyl)propyl)-4-[2-(3-pyridyl)thiazolidine-4-yl-carbonyl]-piperazine;

1-(3-(4'-N-hydroxy-N-propanoyl-aminophenyl)propyl)-4-[2-(3-pyridyl)thiazolidine-4-yl-carbonyl]-piperazine;

1-(3-(4'-N-butanoyl-N-hydroxyaminophenyl)propyl)-4-[2-(3-pyridyl)thiazolidine-4-yl-carbonyl]-piperazine;

1-(3-(3'-N-acetyl-N-hydroxyaminophenyl)propyl)-4-[2-(3-pyridyl)thiazolidine-4-yl-carbonyl]-piperazine;

1-(3-(3'-N-ethanoyl-N-hydroxyaminophenyl)propyl)-4-[2-(3-pyridyl)thiazolidine-4-yl-carbonyl]-piperazine;

1-(3-(3'-N-hydroxy-N-propanoyl-aminophenyl)propyl)-4-[2-(3-pyridyl)thiazolidine-4-yl-carbonyl]-piperazine;

1-(3-(3'-N-butanoyl-N-hydroxyaminophenyl)propyl)-4-[2-(3-pyridyl)thiazolidine-4-yl-carbonyl]-piperazine;

1-(3-(2'-N-acetyl-N-hydroxyaminophenyl)propyl)-4-[2-(3-pyridyl)thiazolidine-4-yl-carbonyl]-piperazine;

1-(3-(2'-N-ethanoyl-N-hydroxyaminophenyl)propyl)-4-[2-(3-pyridyl)thiazolidine-4-yl-carbonyl]-piperazine;

1-(3-(2'-N-hydroxy-N-propanoyl-aminophenyl)propyl)-4-[2-(3-pyridyl)thiazolidine-4-yl-carbonyl]-piperazine; and

1-(3-(2'-N-butanoyl-N-hydroxyaminophenyl)propyl)-4-[2-(3-pyridyl)thiazolidine-4-yl-carbonyl]-piperazine.

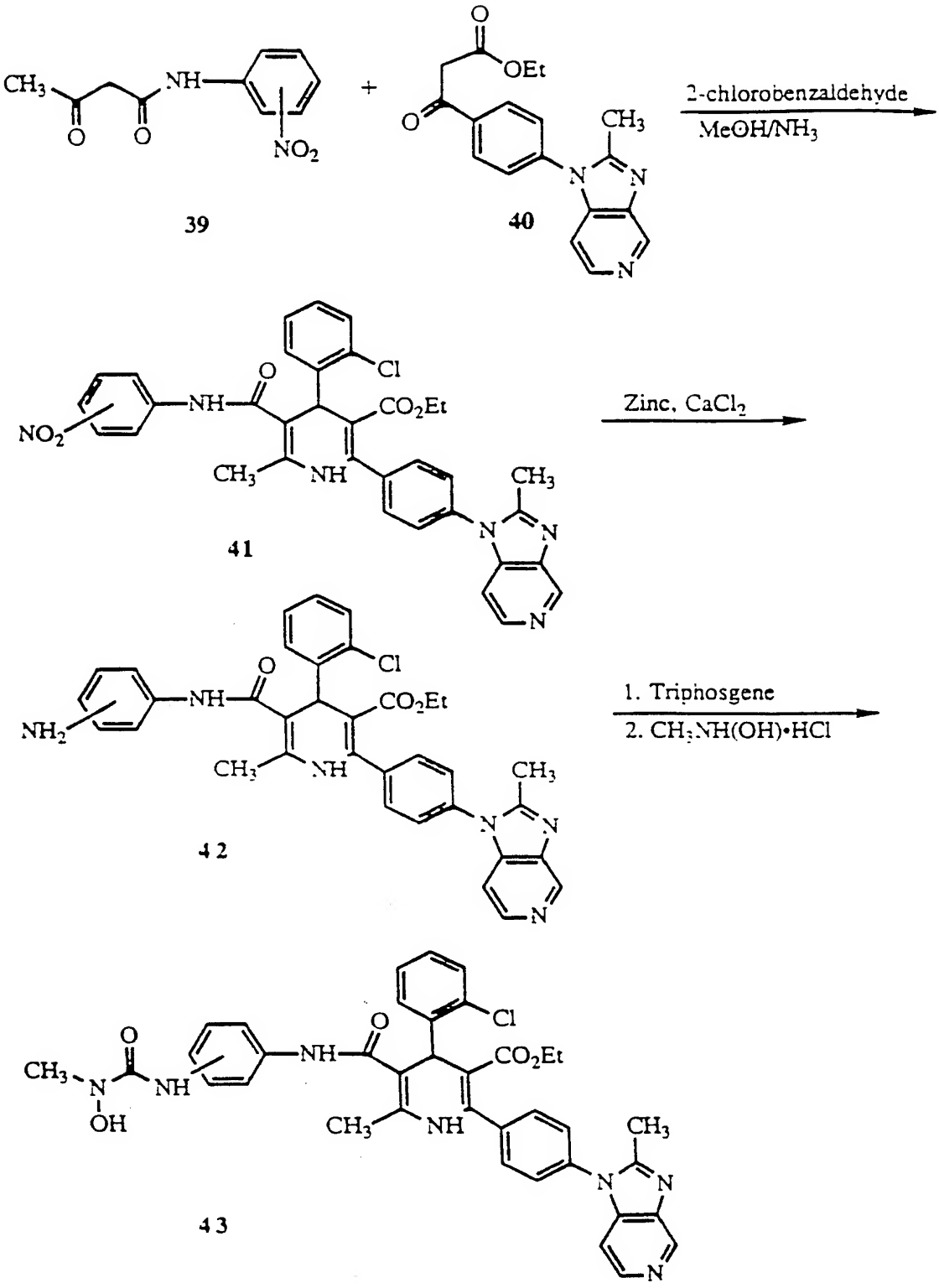
Example 5: Preparation of Dihydropyridines As Dual Function Antagonists

Dihydropyridines with PAF receptor antagonist activity, including those disclosed in UK Patent Application No. 2 233 974 A and WO 90/12015, can be modified to exhibit 5-lipoxygenase inhibiting activity. Nonlimiting examples of dihydropyridines modified to exhibit 5-lipoxygenase inhibiting activity are illustrated in Figure 5. Scheme 5 below illustrates three pathways for the preparation of dual function dihydropyridines. The first pathway sets out the preparation of the hydroxyureidylphenyl dihydropyridine **43**. Reaction of the ketoamide **39** with the ketoester **40** and 2-chlorobenzaldehyde gives the nitroamide **41**. Reduction of the nitroamide with zinc yields the aminoamide **42**. Reaction of the aminoamide with triphosgene and methyl hydroxylamine gives the dual function antagonist **43**.

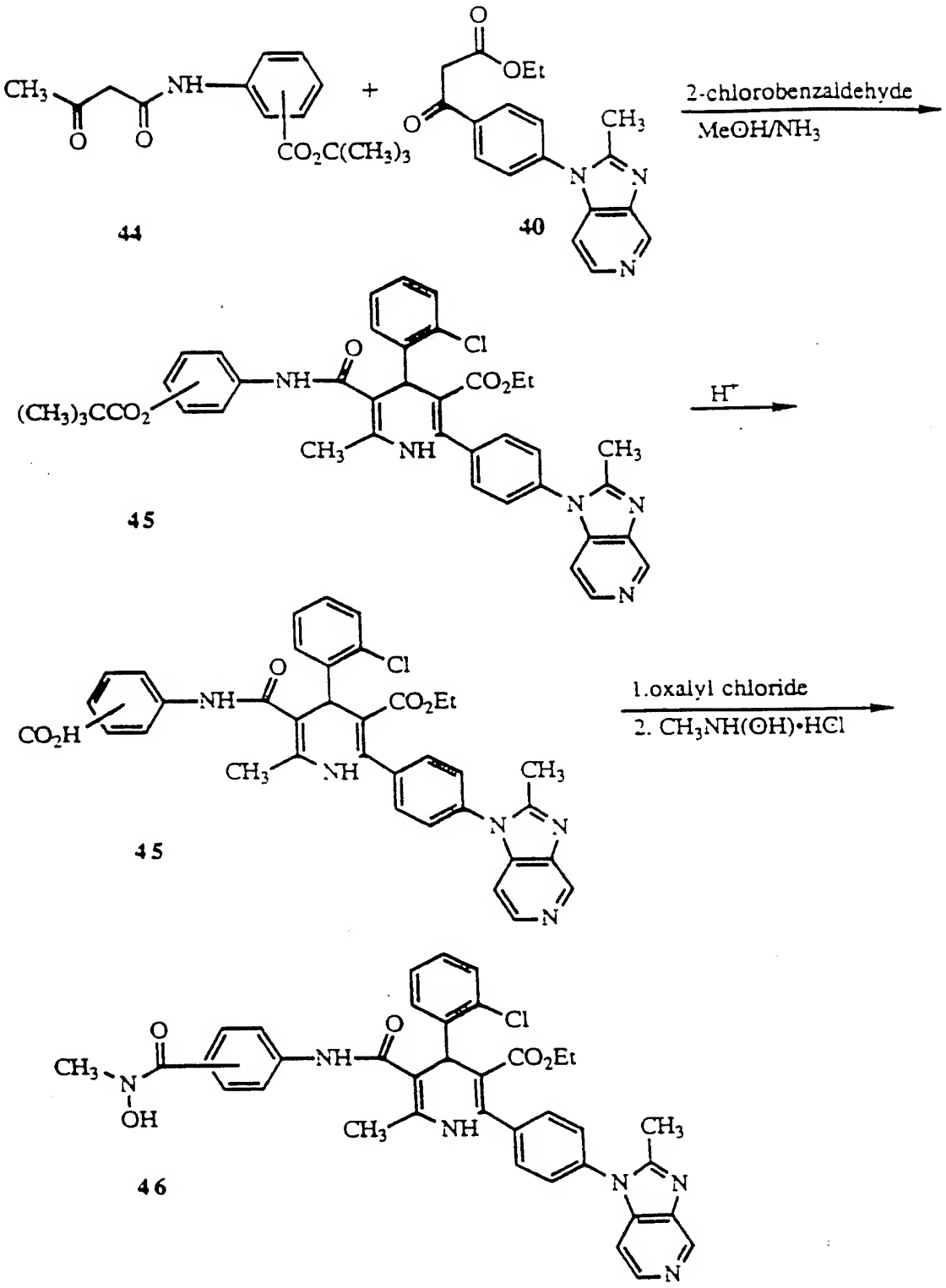
Pathways two and three of Scheme 5 illustrate methods for the preparation of hydroxamidophenyldihydropyridine and hydroxamidodihydropyridine. The hydroxamidophenyldihydropyridine **46** is prepared as described above from the ketoamide **44**, ketoester **40** and

2-chlorobenzaldehyde. The hydroxamidodihydropyridine **50** can be prepared from the ketoesters **47** and **40** along with 2-chlorobenzaldehyde.

Scheme 5

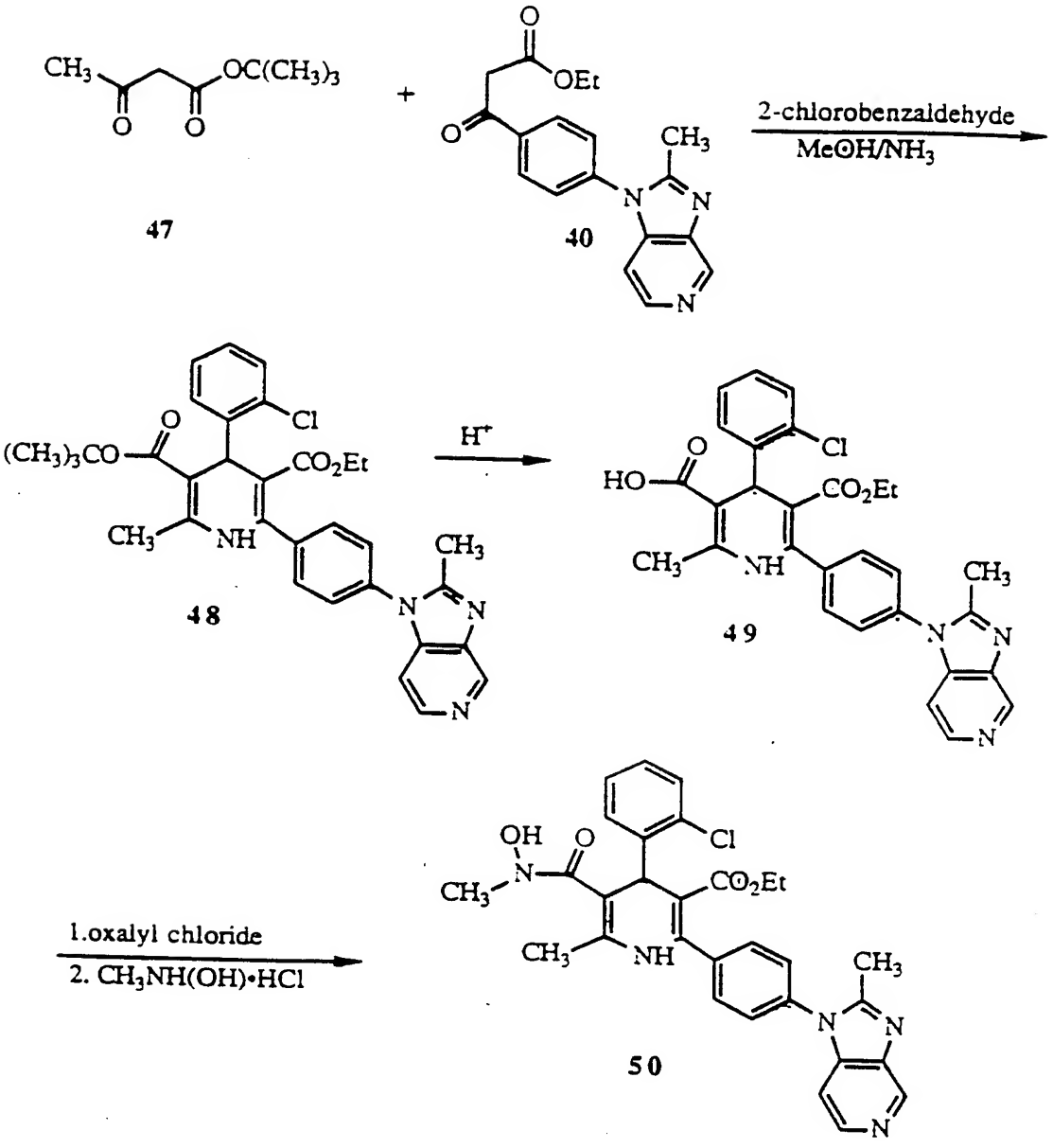

2-chlorobenzaldehyde
MeOH/NH3
39
40
Zinc, CaCl2
41
1. Triphosgene
2. CH3NH(OH)•HCl
42
43

Scheme 5



44 40 45 45 46

Scheme 5


47
40
2-chlorobenzaldehyde
MeOH/NH3
H+
48
49
1.oxalyl chloride
2. CH3NH(OH)•HCl
50

Nonlimiting examples of dual function dihydropyridines that can be prepared according to this process are:

Compound 43 (Hydroxyurea):
4-(2-chlorophenyl)-3-ethoxycarbonyl-5-[(4-N-hydroxy-N-methylureidylphenyl)-aminocarbonyl]-6-methyl-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)-phenyl]-1,4-dihydropyridine;

Derivatives of hydroxamic acid 43:
4-(2-chlorophenyl)-3-ethoxycarbonyl-5-[(4-N-hydroxyureidylphenyl)-aminocarbonyl]-6-methyl-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl]-1,4-dihydropyridine;

4-(2-chlorophenyl)-3-ethoxycarbonyl-5-[(4-N-ethyl-N-hydroxyureidylphenyl)aminocarbonyl]-6-methyl-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl]-1,4-dihydropyridine;

4-(2-chlorophenyl)-3-ethoxycarbonyl-5-[(4-N-hydroxy-N-propylureidylphenyl)aminocarbonyl]-6-methyl-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)-phenyl]-1,4-dihydropyridine;

4-(2-chlorophenyl)-3-ethoxycarbonyl-5-[(4-N-cyclopropyl-N-hydroxyureidylphenyl)aminocarbonyl]-6-methyl-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)-phenyl]-1,4-dihydropyridine;

4-(2-chlorophenyl)-3-ethoxycarbonyl-5-[(3-N-hydroxy-N-methylureidylphenyl)aminocarbonyl]-6-methyl-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)-phenyl]-1,4-dihydropyridine;

4-(2-chlorophenyl)-3-ethoxycarbonyl-5-[(3-N-ethyl-N-hydroxyureidylphenyl)aminocarbonyl]-6-methyl-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl]-1,4-dihydropyridine;

4-(2-chlorophenyl)-3-ethoxycarbonyl-5-[(3-N-benzyl-N-hydroxyureidylphenyl)aminocarbonyl]-6-methyl-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl]-1,4-dihydropyridine;

4-(2-chlorophenyl)-3-ethoxycarbonyl-5-[(3-N-hydroxy-N-propylureidylphenyl)aminocarbonyl]-6-methyl-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)-phenyl]-1,4-dihydropyridine;

4-(2-chlorophenyl)-3-ethoxycarbonyl-5-[(3-N-cyclopropyl-N-hydroxyureidylphenyl)aminocarbonyl]-6-methyl-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)-phenyl]-1,4-dihydropyridine;

4-(2-chlorophenyl)-3-ethoxycarbonyl-5-[(2-N-hydroxy-N-methylureidylphenyl)aminocarbonyl]-6-methyl-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)-phenyl]-1,4-dihydropyridine;

4-(2-chlorophenyl)-3-ethoxycarbonyl-5-[(2-N-ethyl-N-hydroxyureidylphenyl)aminocarbonyl]-6-methyl-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl]-1,4-dihydropyridine;

4-(2-chlorophenyl)-3-ethoxycarbonyl-5-[(2-N-butyl-N-hydroxyureidylphenyl)aminocarbonyl]-6-methyl-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl]-1,4-dihydropyridine;

4-(2-chlorophenyl)-3-ethoxycarbonyl-5-[(2-N-hydroxy-N-propylureidylphenyl)aminocarbonyl]-6-methyl-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)-phenyl]-1,4-dihydropyridine;

4-(2-chlorophenyl)-3-ethoxycarbonyl-5-[(2-N-hydroxy-N-phenylureidylphenyl)aminocarbonyl]-6-methyl-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)-phenyl]-1,4-dihydropyridine;

Reverse hydroxyurea of Compound 43:
4-(2-chlorophenyl)-3-ethoxycarbonyl-5-[(4-N-hydroxy-N'-methylureidylphenyl)-aminocarbonyl]-6-methyl-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)-phenyl]-1,4-dihydropyridine;

Derivatives of Reverse Hydroxyurea of Compound 43:
4-(2-chlorophenyl)-3-ethoxycarbonyl-5-[(4-N-hydroxyureidylphenyl)-aminocarbonyl]-6-methyl-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl]-1,4-dihydropyridine;

4-(2-chlorophenyl)-3-ethoxycarbonyl-5-[(4-N'-ethyl-N-hydroxyureidylphenyl)-aminocarbonyl]-6-methyl-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl]-1,4-dihydropyridine;

4-(2-chlorophenyl)-3-ethoxycarbonyl-5-[(4-N'-cyclopropyl-N-hydroxyureidylphenyl)-aminocarbonyl]-6-methyl-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)-phenyl]-1,4-dihydropyridine;

4-(2-chlorophenyl)-3-ethoxycarbonyl-5-[(4-N'-butyl-N-hydroxyureidylphenyl)-aminocarbonyl]-6-methyl-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl]-1,4-dihydropyridine;

4-(2-chlorophenyl)-3-ethoxycarbonyl-5-[(3-N-hydroxyureidylphenyl)-aminocarbonyl]-6-methyl-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl]-1,4-dihydropyridine;

4-(2-chlorophenyl)-3-ethoxycarbonyl-5-[(3-N-hydroxy-N'-methylureidylphenyl)-aminocarbonyl]-6-methyl-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)-phenyl]-1,4-dihydropyridine;

4-(2-chlorophenyl)-3-ethoxycarbonyl-5-[(3-N'-ethyl-N-hydroxyureidylphenyl)-aminocarbonyl]-6-methyl-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl]-1,4-dihydropyridine;

4-(2-chlorophenyl)-3-ethoxycarbonyl-5-[(3-N-hydroxy-N'-phenylureidylphenyl)-aminocarbonyl]-6-methyl-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)-phenyl]-1,4-dihydropyridine;

4-(2-chlorophenyl)-3-ethoxycarbonyl-5-[(3-N'-cyclopropyl-N-hydroxyureidylphenyl)-aminocarbonyl]-6-methyl-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)-phenyl]-1,4-dihydropyridine;

4-(2-chlorophenyl)-3-ethoxycarbonyl-5-[(2-N-hydroxyureidylphenyl)-aminocarbonyl]-6-methyl-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl]-1,4-dihydropyridine;

4-(2-chlorophenyl)-3-ethoxycarbonyl-5-[(2-N-hydroxy-N'-methylureidylphenyl)-aminocarbonyl]-6-methyl-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)-phenyl]-1,4-dihydropyridine;

4-(2-chlorophenyl)-3-ethoxycarbonyl-5-[(2-N'-ethyl-N-hydroxyureidylphenyl)-aminocarbonyl]-6-methyl-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl]-1,4-dihydropyridine;

4-(2-chlorophenyl)-3-ethoxycarbonyl-5-[(2-N-hydroxy-N'-propylureidylphenyl)-aminocarbonyl]-6-methyl-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)-phenyl]-1,4-dihydropyridine;

4-(2-chlorophenyl)-3-ethoxycarbonyl-5-[(2-N'-butyl-N-hydroxyureidylphenyl)-aminocarbonyl]-6-methyl-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl]-1,4-dihydropyridine;

Compound 46 (Hydroxamic Acid):
4-(2-chlorophenyl)-3-ethoxycarbonyl-5-[(4-N-hydroxy-N-methylcarboxamidophenyl)-aminocarbonyl]-6-methyl-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)-phenyl]-1,4-dihydropyridine;

Derivatives of Hydroxamic acid 46:
4-(2-chlorophenyl)-3-ethoxycarbonyl-5-[(4-N-hydroxycarboxamidophenyl)aminocarbonyl]-6-methyl-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl]-1,4-dihydropyridine;

4-(2-chlorophenyl)-3-ethoxycarbonyl-5-[(4-N-ethyl-N-hydroxycarboxamidophenyl)aminocarbonyl]-6-methyl-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl]-1,4-dihydropyridine;

4-(2-chlorophenyl)-3-ethoxycarbonyl-5-[(4-N-hydroxy-N-propylcarboxamidophenyl)aminocarbonyl]-6-methyl-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)-phenyl]-1,4-dihydropyridine;

4-(2-chlorophenyl)-3-ethoxycarbonyl-5-[(4-N-butyl-N-hydroxycarboxamidophenyl)aminocarbonyl]-6-methyl-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl]-1,4-dihydropyridine;

4-(2-chlorophenyl)-3-ethoxycarbonyl-5-[(3-N-hydroxycarboxamidophenyl)-aminocarbonyl]-6-methyl-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl]-1,4-dihydropyridine;

4-(2-chlorophenyl)-3-ethoxycarbonyl-5-[(3-N-hydroxy-N-methylcarboxamidophenyl)aminocarbonyl]-6-methyl-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)-phenyl]-1,4-dihydropyridine;

4-(2-chlorophenyl)-3-ethoxycarbonyl-5-[(3-N-ethyl-N-hydroxycarboxamidophenyl)aminocarbonyl]-6-methyl-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl]-1,4-dihydropyridine;

4-(2-chlorophenyl)-3-ethoxycarbonyl-5-[(3-N-hydroxy-N-propylcarboxamidophenyl)aminocarbonyl]-6-methyl-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)-phenyl]-1,4-dihydropyridine;

4-(2-chlorophenyl)-3-ethoxycarbonyl-5-[(3-N-cyclopropyl-N-hydroxycarboxamidophenyl)amino-carbonyl]-6-methyl-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl]-1,4-dihydropyridine;

4-(2-chlorophenyl)-3-ethoxycarbonyl-5-[(2-N-hydroxycarboxamidophenyl)aminocarbonyl]-6-methyl-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl]-1,4-dihydropyridine;

4-(2-chlorophenyl)-3-ethoxycarbonyl-5-[(2-N-hydroxy-N-methylcarboxamidophenyl)aminocarbonyl]-6-methyl-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)-phenyl]-1,4-dihydropyridine;

4-(2-chlorophenyl)-3-ethoxycarbonyl-5-[(2-N-ethyl-N-hydroxycarboxamidophenyl)aminocarbonyl]-6-methyl-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl]-1,4-dihydropyridine;

4-(2-chlorophenyl)-3-ethoxycarbonyl-5-[(2-N-hydroxy-N-propylcarboxamidophenyl)aminocarbonyl]-6-methyl-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)-phenyl]-1,4-dihydropyridine;

4-(2-chlorophenyl)-3-ethoxycarbonyl-5-[(2-N-butyl-N-hydroxycarboxamidophenyl)aminocarbonyl]-6-methyl-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl]-1,4-dihydropyridine;

Reverse Hydroxamic Acid of Compound 46:

4-(2-chlorophenyl)-3-ethoxycarbonyl-5-[(4-N-acetyl-N-hydroxyaminophenyl)-aminocarbonyl]-6-methyl-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl]-1,4-dihydropyridine;

4-(2-chlorophenyl)-3-ethoxycarbonyl-5-[(4-N-ethanoyl-N-hydroxyaminophenyl)-aminocarbonyl]-6-methyl-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)-phenyl]-1,4-dihydropyridine;

4-(2-chlorophenyl)-3-ethoxycarbonyl-5-[(4-N-hydroxy-N-propanoylaminophenyl)-aminocarbonyl]-6-methyl-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)-phenyl]-1,4-dihydropyridine;

4-(2-chlorophenyl)-3-ethoxycarbonyl-5-[(4-N-

butanoyl-N-hydroxyaminophenyl)-aminocarbonyl]-6-methyl-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)-phenyl]-1,4-dihydropyridine;

4-(2-chlorophenyl)-3-ethoxycarbonyl-5-[(3-N-acetyl-N-hydroxyaminophenyl)-aminocarbonyl]-6-methyl-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl]-1,4-dihydropyridine;

4-(2-chlorophenyl)-3-ethoxycarbonyl-5-[(3-N-ethanoyl-N-hydroxyaminophenyl)-aminocarbonyl]-6-methyl-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)-phenyl]-1,4-dihydropyridine;

4-(2-chlorophenyl)-3-ethoxycarbonyl-5-[(3-N-hydroxy-N-propanoylaminophenyl)-aminocarbonyl]-6-methyl-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)-phenyl]-1,4-dihydropyridine;

4-(2-chlorophenyl)-3-ethoxycarbonyl-5-[(3-N-butanoyl-N-hydroxyaminophenyl)-aminocarbonyl]-6-methyl-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)-phenyl]-1,4-dihydropyridine;

4-(2-chlorophenyl)-3-ethoxycarbonyl-5-[(2-N-acetyl-N-hydroxyaminophenyl)-aminocarbonyl]-6-methyl-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl]-1,4-dihydropyridine;

4-(2-chlorophenyl)-3-ethoxycarbonyl-5-[(2-N-ethanoyl-N-hydroxyaminophenyl)-aminocarbonyl]-6-methyl-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)-phenyl]-1,4-dihydropyridine;

4-(2-chlorophenyl)-3-ethoxycarbonyl-5-[(2-N-hydroxy-N-propanoylaminophenyl)-aminocarbonyl]-6-methyl-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)-phenyl]-1,4-dihydropyridine;

4-(2-chlorophenyl)-3-ethoxycarbonyl-5-[(2-N-butanoyl-N-hydroxyaminophenyl)-aminocarbonyl]-6-methyl-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)-phenyl]-1,4-dihydropyridine;

Compound 50 (Hydroxamic Acid):

4-(2-chlorophenyl)-3-ethoxycarbonyl-5-[4-N-hydroxy-N-methylcarboxamido]-6-methyl-2-[4-(2-methyl-imidazo[4,5-c]pyrid-1-yl)phenyl]-1,4-dihydro-pyridine;

Derivatives of Hydroxamic Acid 50:

4-(2-chlorophenyl)-3-ethoxycarbonyl-5-[4-N-hydroxy-carboxamido]-6-methyl-2-[4-(2-methylimidazo[4,5-c]-pyrid-1-yl)phenyl]-1,4-dihydropyridine;

4-(2-chlorophenyl)-3-ethoxycarbonyl-5-[4-N-ethyl-N-hydroxycarboxamido]-6-methyl-2-[4-(2-methylimidazo-[4,5-c]pyrid-1-yl)phenyl]-1,4-dihydropyridine;

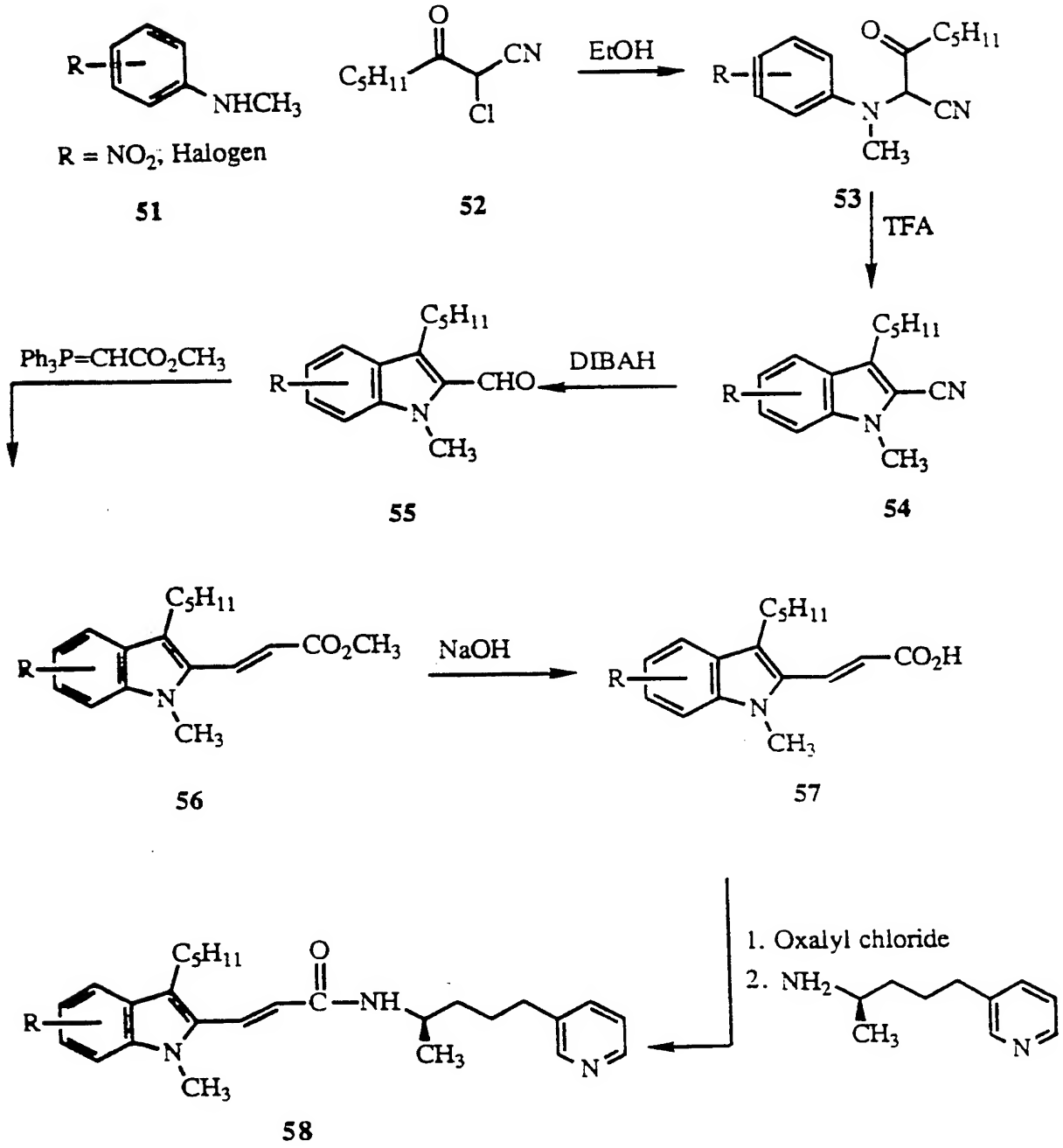
4-(2-chlorophenyl)-3-ethoxycarbonyl-5-[4-N-hydroxy-N-phenylcarboxamido]-6-methyl-2-[4-(2-methyl-imidazo[4,5-c]pyrid-1-yl)phenyl]-1,4-dihydro-pyridine; and

4-(2-chlorophenyl)-3-ethoxycarbonyl-5-[4-N-butyl-N-hydroxycarboxamido]-6-methyl-2-[4-(2-methylimidazo-[4,5-c]pyrid-1-yl)phenyl]-1,4-dihydropyridine.

Example 6: Preparation of Propenyl Carboxamide Hydroxyurea and Hydroxamic acid Derivatives with PAF Receptor Antagonist Activity and 5-Lipoxygenase Inhibiting Activity.

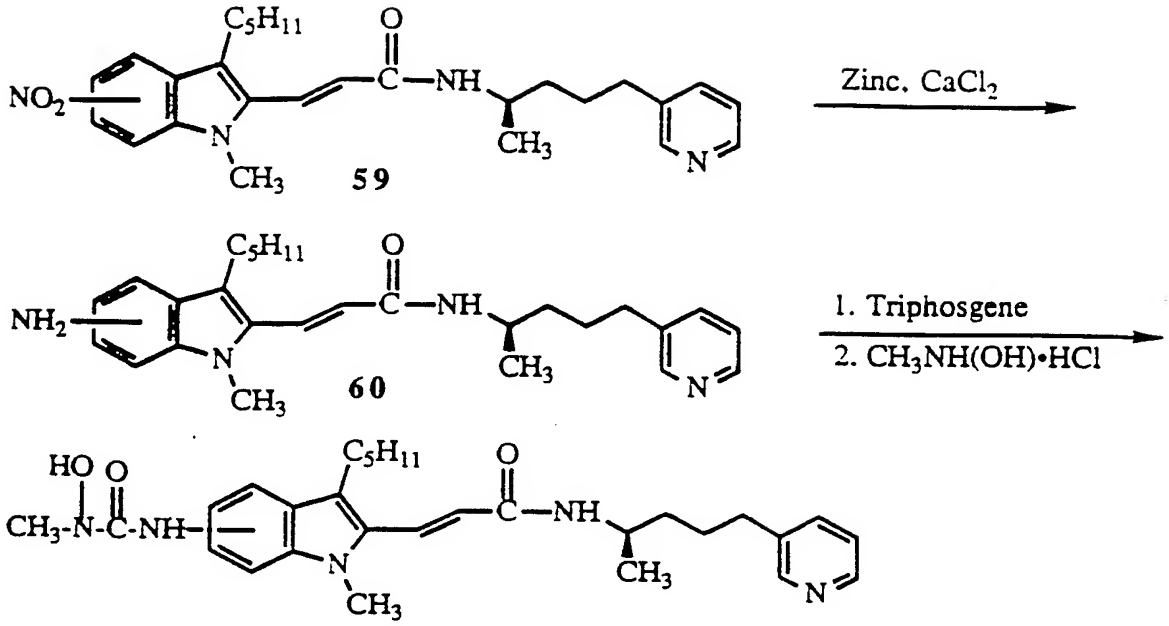
Propenyl carboxamides with PAF receptor antagonist activity can be modified into dual function antagonists with 5-lipoxygenase inhibiting activity, including those disclosed in Gutherie, G. L., et al., J. Med. Chem., 33, 2857 (1990); and European Patent Application No. 298466 A2. Examples of propenyl carboxamides with dual function PAF receptor antagonism and 5-LO inhibiting activity are illustrated in Figure 6. These compounds can be synthesized as illustrated in Scheme 6 below. The nitro or halogenoaniline **51** is reacted with the nitrile **52** to give the aniline **53**. Ring closure under acidic conditions then gives the indole **54**. The nitrile moiety of indole **54** is reduced with diisobutylaluminum hydride to give the aldehyde **55**. Conversion of the aldehyde **55** to the olefin with the Horner-Emmons Reagent gives the ester **56** which is then hydrolyzed to the acid **57**. Amidation of **57** through the acid chloride with R-3-(4-aminopentyl)pyridine (shown in scheme 6) gives the amide **58**. When R is a nitro group as in **59**, it is reduced with zinc metal to the amine and then converted to the hydroxyurea **61** with triphosgene and methyl hydroxylamine. When R is halogen as in **62** the aromatic ring can be metalated and carboxylated to produce the acid **63**. Conversion to the acid chloride and treatment with methyl hydroxylamine then yields the hydroxamic acid **64**.

Scheme 6

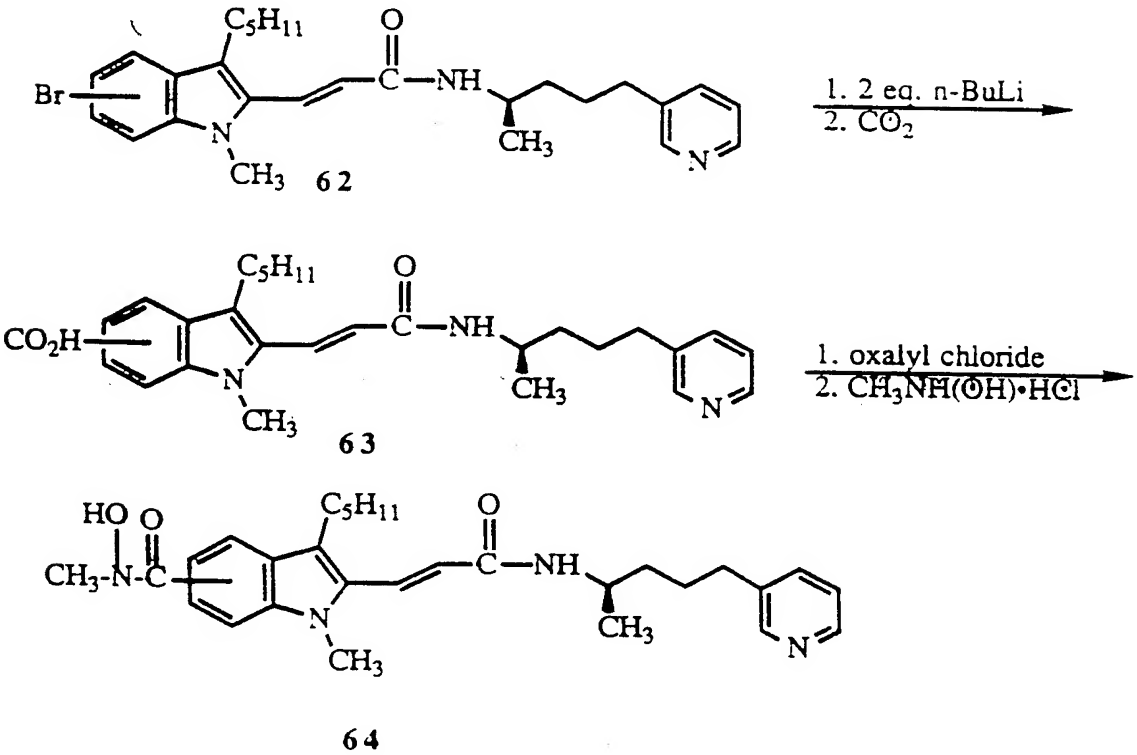

R
NHCH3
R = NO2; Halogen
51
C5H11
CN
Cl
52
EtOH
C5H11
CN
CH3
53
TFA
C5H11
CN
CH3
54
DIBAH
C5H11
CHO
CH3
55
Ph3P=CHCO2CH3
C5H11
CO2CH3
CH3
56
NaOH
C5H11
CO2H
CH3
57
1. Oxalyl chloride
2. NH2
C5H11
O
NH
CH3
N
CH3
58

Scheme 6

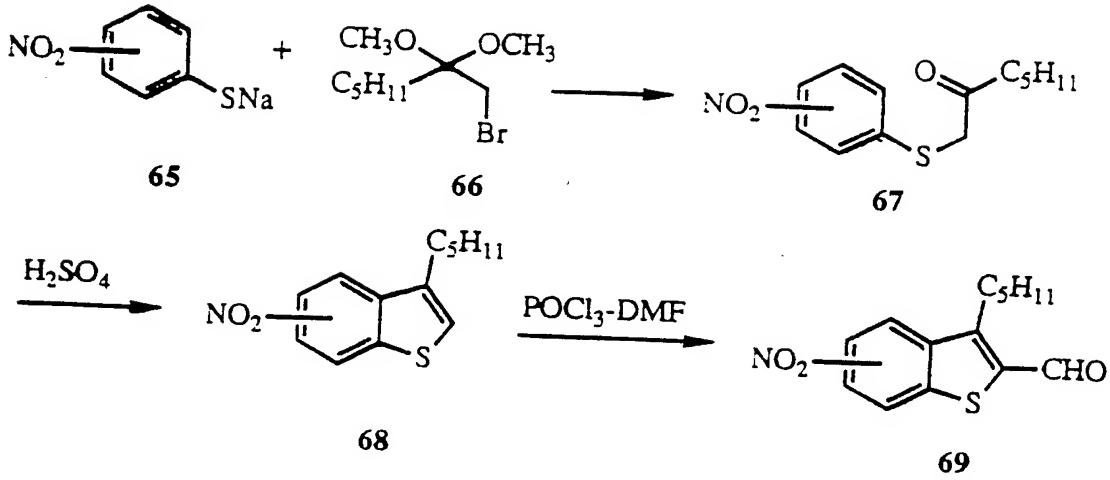
Hydroxyureas:



Hydroxamates:

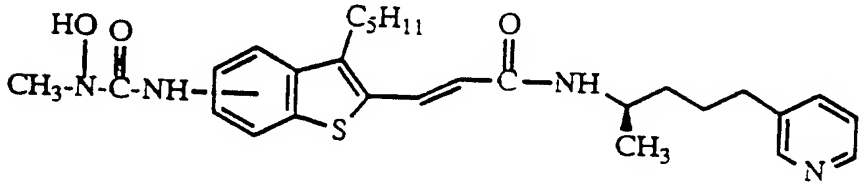


Scheme 6

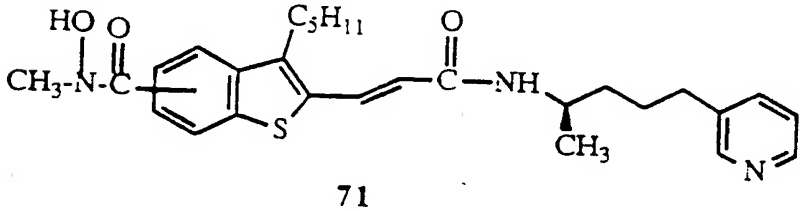


65 66 67 68 69

Following the same methodology as for the indole series (i.e. I), benzothiophene II can be converted to the following hydroxamates and hydroxyureas.



70



71

In a similar fashion, thiophene analogues can be prepared as shown in **65** through **69**. These in turn can be converted to the hydroxyureas such as **70** or the hydroxamic acids such as **71**.

Nonlimiting examples of dual function propenyl carboxamides that can be prepared according to this process are:

Compound 61 (Hydroxyurea):

[R-(E)]-6-(N-hydroxy-N-methylureidyl)-3-pentyl-1-methyl-2-indole-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

Derivatives of Hydroxyurea 61:

[R-(E)]-6-(N-hydroxyureidyl)-3-pentyl-1-methyl-2-indole-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

[R-(E)]-6-(N-ethyl-N-hydroxyureidyl)-3-pentyl-1-methyl-2-indole-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

[R-(E)]-6-(N-hydroxy-N-phenylureidyl)-3-pentyl-1-methyl-2-indole-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

[R-(E)]-6-(N-butyl-N-hydroxyureidyl)-3-pentyl-1-methyl-2-indole-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

[R-(E)]-7-(N-hydroxyureidyl)-3-pentyl-1-methyl-2-indole-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

[R-(E)]-7-(N-hydroxy-N-methylureidyl)-3-pentyl-1-methyl-2-indole-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

[R-(E)]-7-(N-benzyl-N-hydroxyureidyl)-3-pentyl-1-methyl-2-indole-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

[R-(E)]-7-(N-hydroxy-N-propylureidyl)-3-pentyl-1-methyl-2-indole-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

[R-(E)]-7-(N-butyl-N-hydroxyureidyl)-3-pentyl-1-methyl-2-indole-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

[R-(E)]-4-(N-hydroxyureidyl)-3-pentyl-1-methyl-2-indole-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

[R-(E)]-4-(N-hydroxy-N-methylureidyl)-3-pentyl-1-methyl-2-indole-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

[R-(E)]-4-(N-ethyl-N-hydroxyureidyl)-3-pentyl-1-methyl-2-indole-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

[R-(E)]-4-(N-hydroxy-N-propylureidyl)-3-pentyl-1-methyl-2-indole-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

[R-(E)]-4-(N-butyl-N-hydroxyureidyl)-3-pentyl-1-methyl-2-indole-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

[R-(E)]-5-(N-hydroxyureidyl)-3-pentyl-1-methyl-2-indole-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

[R-(E)]-5-(N-hydroxy-N-methylureidyl)-3-pentyl-1-methyl-2-indole-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

[R-(E)]-5-(N-ethyl-N-hydroxyureidyl)-3-pentyl-1-methyl-2-indole-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

[R-(E)]-5-(N-hydroxy-N-propylureidyl)-3-pentyl-1-methyl-2-indole-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

[R-(E)]-5-(N-butyl-N-hydroxyureidyl)-3-pentyl-1-methyl-2-indole-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

Reverse Hydroxyurea of Compound 61:

[R-(E)]-6-(N'-ethyl-N-hydroxyureidyl)-3-pentyl-1-methyl-2-indole-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

Derivatives of Reverse Hydroxyurea of Compound 61:

[R-(E)]-6-(N-hydroxyureidyl)-3-pentyl-1-methyl-2-indole-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

[R-(E)]-6-(N'-benzyl-N-hydroxyureidyl)-3-pentyl-1-methyl-2-indole-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

[R-(E)]-6-(N'-p-chlorophenyl-N-hydroxyureidyl)-3-pentyl-1-methyl-2-indole-N-[1-methyl-4-(3-pyridyl)-butyl]-2-propenamide;

[R-(E)]-6-(N'-butyl-N-hydroxyureidyl)-3-pentyl-1-methyl-2-indole-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

[R-(E)]-7-(N-hydroxyureidyl)-3-pentyl-1-methyl-2-indole-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

[R-(E)]-7-(N'-cyclopropyl-N-hydroxyureidyl)-3-pentyl-1-methyl-2-indole-N-[1-methyl-4-(3-pyridyl)-butyl]-2-propenamide;

[R-(E)]-7-(N'-ethyl-N-hydroxyureidyl)-3-pentyl-1-methyl-2-indole-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

[R-(E)]-7-(N'-butylamido)-N-hydroxyureidyl)-3-pentyl-1-methyl-2-indole-N-[1-methyl-4-(3-pyridyl)-butyl]-2-propenamide;

[R-(E)]-4-(N-hydroxyureidyl)-3-pentyl-1-methyl-2-indole-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

[R-(E)]-4-(N'-ethyl-N-hydroxyureidyl)-3-pentyl-1-methyl-2-indole-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

[R-(E)]-4-(N'-benzyl-N-hydroxyureidyl)-3-pentyl-1-methyl-2-indole-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

[R-(E)]-4-(N'-butyl-N-hydroxyureidyl)-3-pentyl-1-methyl-2-indole-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

[R-(E)]-5-(N-hydroxyureidyl)-3-pentyl-1-methyl-2-indole-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

[R-(E)]-5-(N'-cyclopropyl-N-hydroxyureidyl)-3-pentyl-1-methyl-2-indole-N-[1-methyl-4-(3-pyridyl)-butyl]-2-propenamide;

[R-(E)]-5-(N'-ethyl-N-hydroxyureidyl)-3-pentyl-1-methyl-2-indole-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

[R-(E)]-5-(N'-butyl-N-hydroxyureidyl)-3-pentyl-1-methyl-2-indole-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

Compound 64 (Hydroxamic Acid):
[R-(E)]-6-(N-hydroxy-N-methylcarboxamido)-3-pentyl-1-methyl-2-indole-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

5-[4'-(3-(N-hydroxy-N-methylureidylmethyl)-4,5-dimethoxyphenylethyl)phenyl]-2,3-dihydroimidazo-[2,1-a]isoquinoline;

Compound 70 (Hydroxyurea):
[R-(E)]-6-(N-hydroxy-N-methylureidyl)-3-pentyl-2-benzo[b]thiophene-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

Derivatives of Hydroxyurea 70:
[R-(E)]-6-(N-hydroxyureidyl)-3-pentyl-2-benzo[b]-thiophene-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

[R-(E)]-6-(N-ethyl-N-hydroxyureidyl)-3-pentyl-2-benzo[b]thiophene-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

[R-(E)]-6-(N-hydroxy-N-propylureidyl)-3-pentyl-2-benzo[b]thiophene-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

[R-(E)]-6-(N-cyclopropyl-N-hydroxyureidyl)-3-pentyl-2-benzo[b]thiophene-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

[R-(E)]-7-(N-hydroxyureidyl)-3-pentyl-2-benzo[b]-thiophene-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

[R-(E)]-7-(N-hydroxy-N-methylureidyl)-3-pentyl-2-benzo[b]thiophene-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

[R-(E)]-7-(N-ethyl-N-hydroxyureidyl)-3-pentyl-2-benzo[b]thiophene-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

[R-(E)]-7-(N-hydroxy-N-propylureidyl)-3-pentyl-2-benzo[b]thiophene-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

[R-(E)]-7-(N-butyl-N-hydroxyureidyl)-3-pentyl-2-benzo[b]thiophene-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

[R-(E)]-4-(N-hydroxyureidyl)-3-pentyl-2-benzo[b]-thiophene-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

[R-(E)]-4-(N-hydroxy-N-methylureidyl)-3-pentyl-2-benzo[b]thiophene-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

[R-(E)]-4-(N-ethyl-N-hydroxyureidyl)-3-pentyl-2-benzo[b]thiophene-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

[R-(E)]-4-(N-hydroxy-N-propylureidyl)-3-pentyl-2-benzo[b]thiophene-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

[R-(E)]-4-(N-cyclopropyl-N-hydroxyureidyl)-3-pentyl-2-benzo[b]thiophene-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

[R-(E)]-5-(N-hydroxyureidyl)-3-pentyl-2-benzo[b]-thiophene-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

[R-(E)]-5-(N-hydroxy-N-methylureidyl)-3-pentyl-2-benzo[b]thiophene-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

[R-(E)]-5-(N-ethyl-N-hydroxyureidyl)-3-pentyl-2-benzo[b]thiophene-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

[R-(E)]-5-(N-hydroxy-N-propylureidyl)-3-pentyl-2-benzo[b]thiophene-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

[R-(E)]-5-(N-butyl-N-hydroxyureidyl)-3-pentyl-2-benzo[b]thiophene-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

Reverse Hydroxyurea of Compound 70:
[R-(E)]-6-(N-hydroxy-N'-methylureidyl)-3-pentyl-2-benzo[b]thiophene-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

Derivatives of Reverse Hydroxyurea of Compound 70:
[R-(E)]-6-(N-hydroxyureidyl)-3-pentyl-2-benzo[b]-thiophene-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

[R-(E)]-6-(N'-ethyl-N-hydroxyureidyl)-3-pentyl-2-benzo[b]thiophene-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

[R-(E)]-6-((N-hydroxy-N'propylureidyl)-3-pentyl-2-benzo[b]thiophene-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

[R-(E)]-6-(N'-cyclopropyl-N-hydroxyureidyl)-3-pentyl-2-benzo[b]thiophene-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

[R-(E)]-7-(N-hydroxyureidyl)-3-pentyl-2-benzo[b]-thiophene-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

[R-(E)]-7-(N-hydroxy-N'-methylureidyl)-3-pentyl-2-benzo[b]thiophene-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

[R-(E)]-7-(N'-ethyl-N-hydroxyureidyl)-3-pentyl-2-benzo[b]thiophene-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

[R-(E)]-7-(N-hydroxy-N'-propylureidyl)-3-pentyl-2-benzo[b]thiophene-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

[R-(E)]-7-(N'-butyl-N-hydroxyureidyl)-3-pentyl-2-benzo[b]thiophene-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

[R-(E)]-4-(N-hydroxyureidyl)-3-pentyl-2-benzo[b]-thiophene-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

[R-(E)]-4-(N'-ethyl-N-hydroxyureidyl)-3-pentyl-2-benzo[b]thiophene-N-[1-methyl-4-(3-pyridyl)benzyl]-2-propenamide;

[R-(E)]-4-(N'-benzyl-N-hydroxyureidyl)-3-pentyl-2-benzo[b]thiophene-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

[R-(E)]-4-(N'-cyclopropyl-N-hydroxyureidyl)-3-pentyl-2-benzo[b]thiophene-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

[R-(E)]-4-(N'-butyl-N-hydroxyureidyl)-3-pentyl-2-benzo[b]thiophene-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

[R-(E)]-5-(N-hydroxyureidyl)-3-pentyl-2-benzo[b]-thiophene-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

[R-(E)]-5-(N-hydroxy-N'-methylureidyl)-3-pentyl-2-benzo[b]thiophene-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

[R-(E)]-5-(N'-ethyl-N-hydroxyureidyl)-3-pentyl-2-benzo[b]thiophene-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

[R-(E)]-5-(N'-cyclopropyl-N-hydroxyureidyl)-3-pentyl-2-benzo[b]thiophene-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

[R-(E)]-5-(N'-butyl-N-hydroxyureidyl)-3-pentyl-2-

benzo[b]thiophene-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

Compound 71 (Hydroxamic Acid):
[R-(E)]-6-(N-hydroxy-N-methylcarboxamido)-3-pentyl-2-benzo[b]thiophene-N-[1-methyl-4-(3-pyridyl)-butyl]-2-propenamide;

Derivatives of Hydroxamic Acid 71:
[R-(E)]-6-(N-hydroxycarboxamido)-3-pentyl-2-benzo-[b]thiophene-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

R-(E)]-6-(N-benzyl-N-hydroxycarboxamido)-3-pentyl-2-benzo[b]thiophene-N-[1-methyl-4-(3-pyridyl)-butyl]-2-propenamide;

R-(E)]-6-(N-hydroxy-N-propylcarboxamido)-3-pentyl-2-benzo[b]thiophene-N-[1-methyl-4-(3-pyridyl)-butyl]-2-propenamide;

R-(E)]-6-(N-butyl-N-hydroxycarboxamido)-3-pentyl-2-benzo[b]thiophene-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

[R-(E)]-7-(N-hydroxycarboxamido)-3-pentyl-2-benzo-[b]thiophene-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

[R-(E)]-7-(N-hydroxy-N-methylcarboxamido)-3-pentyl-2-benzo[b]thiophene-N-[1-methyl-4-(3-pyridyl)-butyl]-2-propenamide;

R-(E)]-7-(N-ethyl-N-hydroxycarboxamido)-3-pentyl-2-benzo[b]thiophene-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

R-(E)]-7-(N-hydroxy-N-propylcarboxamido)-3-pentyl-2-benzo[b]thiophene-N-[1-methyl-4-(3-pyridyl)-butyl]-2-propenamide;

R-(E)]-7-(N-butyl-N-hydroxycarboxamido)-3-pentyl-2-benzo[b]thiophene-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

[R-(E)]-4-(N-hydroxycarboxamido)-3-pentyl-2-benzo-[b]thiophene-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

[R-(E)]-4-(N-hydroxy-N-methylcarboxamido)-3-pentyl-2-benzo[b]thiophene-N-[1-methyl-4-(3-pyridyl)-butyl]-2-propenamide;

R-(E)]-4-(N-ethyl-N-hydroxycarboxamido)-3-pentyl-2-benzo[b]thiophene-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

R-(E)]-4-(N-hydroxy-N-propylcarboxamido)-3-pentyl-2-benzo[b]thiophene-N-[1-methyl-4-(3-pyridyl)-butyl]-2-propenamide;

R-(E)]-4-(N-butyl-N-hydroxycarboxamido)-3-pentyl-2-benzo[b]thiophene-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

[R-(E)]-5-(N-hydroxycarboxamido)-3-pentyl-2-benzo-[b]thiophene-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide;

[R-(E)]-5-(N-hydroxy-N-methylcarboxamido)-3-pentyl-2-benzo[b]thiophene-N-[1-methyl-4-(3-pyridyl)-butyl]-2-propenamide;

R-(E)]-5-(N-benzyl-N-hydroxycarboxamido)-3-pentyl-2-benzo[b]thiophene-N-[1-methyl-4-(3-pyridyl)-butyl]-2-propenamide;

R-(E)]-5-(N-hydroxy-N-propylcarboxamido)-3-pentyl-2-benzo[b]thiophene-N-[1-methyl-4-(3-pyridyl)-butyl]-2-propenamide; and

R-(E)]-5-(N-butyl-N-hydroxycarboxamido)-3-pentyl-2-benzo[b]thiophene-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide.

Example 7: Preparation of Hydroxyurea and Hydroxamic Acid Derivatives of Kadsurenone Analogs with PAF Receptor Antagonist Activity and 5-Lipoxygenase Inhibiting Activity.

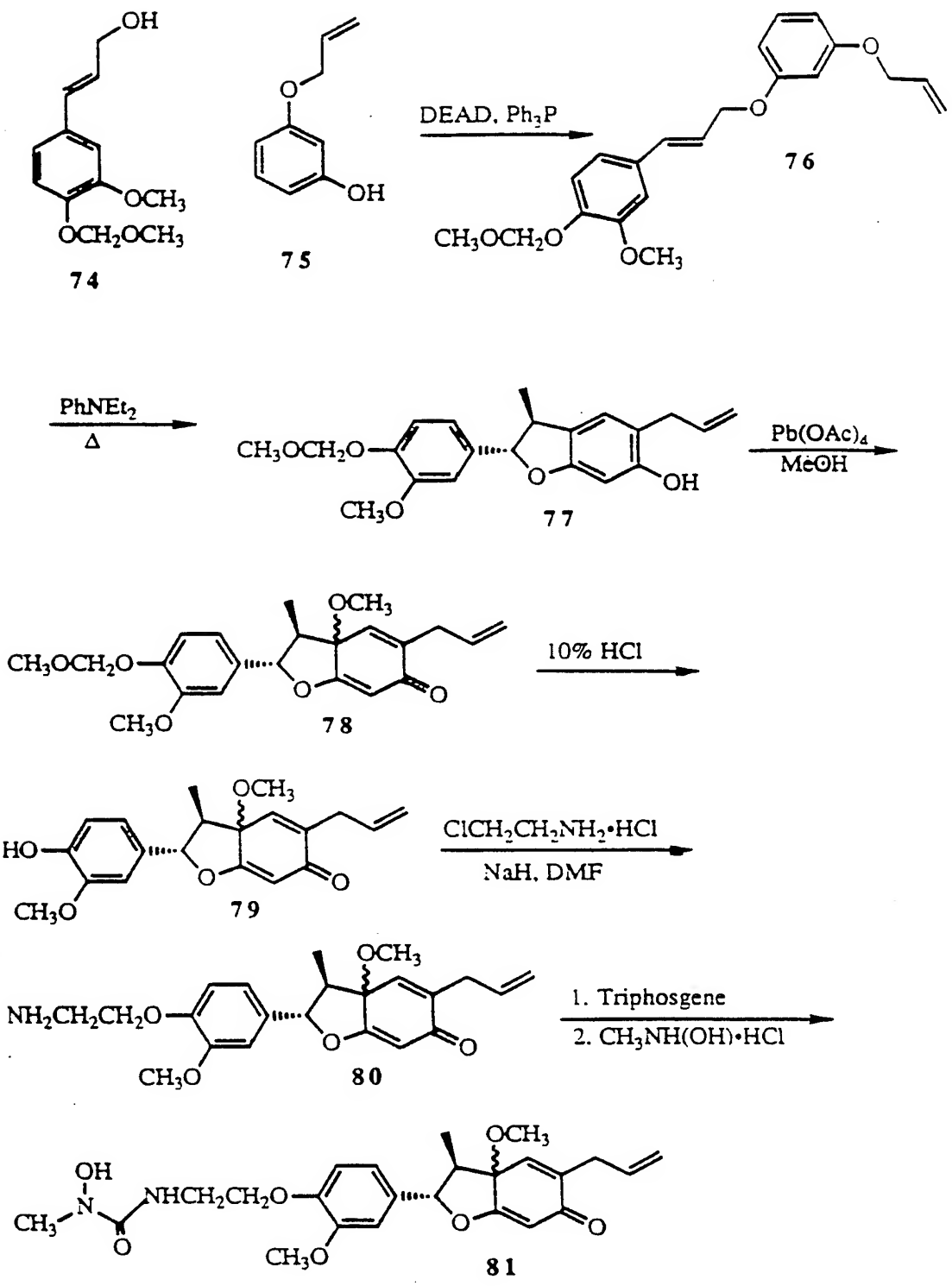
Kadsurenone derivatives with PAF receptor antagonist activity, including those reported in Shen, et al., Proc. Natl. Acad. Sci. U.S.A., 82, 672(1985) and Ponpipom, et al., J. Med. Chem., 30, 136 (1987) can be converted into dual function antagonists by the addition of R' groups at bulk tolerating areas on the molecule. Examples of kadsurenone derivatives modified to exhibit 5-lipoxygenase activity according to the present invention are illustrated in Figures 7 and 7a. Processes for the preparation of compounds illustrated in Figures 7 and 7a are set out in Schemes 7 and 7a, respectively, below.

Referring to Scheme 7, kadsurenone derivative **81** is prepared from allylic alcohol **74** and phenol **75** to give the diaryl ether **76**. Cyclization of **76** with diethylaniline provides the dihydrobenzofuran **77** which is subsequently oxidized with lead tetraacetate to give the derivative **78**. Removal of the ether protecting group yields the phenol **79**. Reaction of the sodium salt of phenol

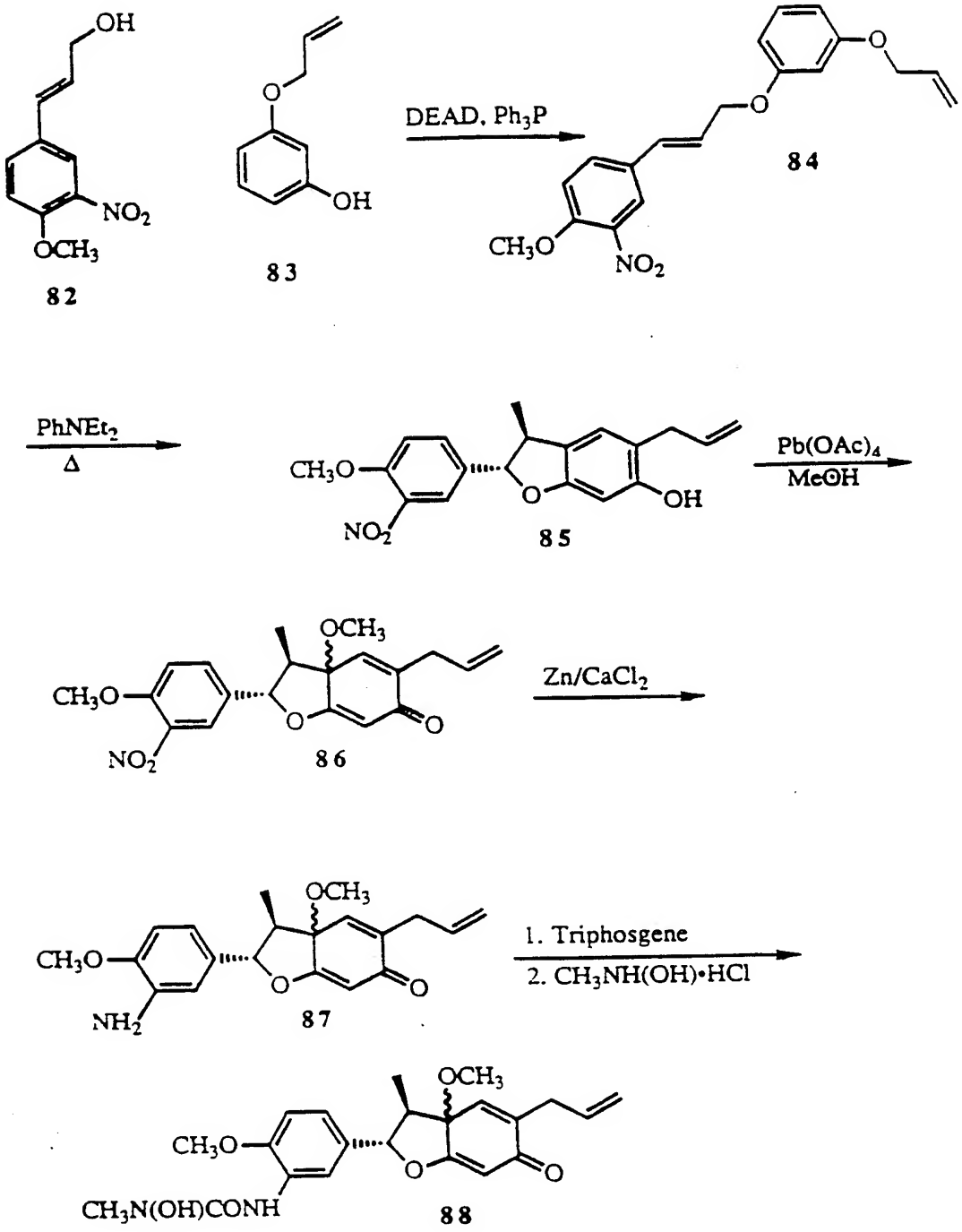
79 with chloroethylamine gives the amine 80 which is converted to the hydroxyurea 81 in the standard manner.

Referring to Figure 7a, kadsurenone derivative 88 is prepared from the allylic alcohol 82 and the phenol 83 as illustrated.

Scheme 7


OH
OCH3
OCH2OCH3
74
O
OH
75
DEAD, Ph3P
O
O
76
CH3OCH2O
OCH3
PhNEt2
Δ
CH3OCH2O
CH3O
O
OH
77
Pb(OAc)4
MeOH
OCH3
CH3OCH2O
CH3O
O
O
78
10% HCl
OCH3
HO
CH3O
O
O
79
ClCH2CH2NH2•HCl
NaH, DMF
OCH3
NH2CH2CH2O
CH3O
O
O
80
1. Triphosgene
2. CH3NH(OH)•HCl
OCH3
OH
CH3
N
O
NHCH2CH2O
CH3O
O
O
81

Scheme 7a


OH
NO2
OCH3
82
O
OH
83
DEAD, Ph3P
O
O
84
CH3O
NO2
PhNEt2
Δ
CH3O
NO2
O
OH
85
Pb(OAc)4
MeOH
OCH3
CH3O
NO2
O
O
86
Zn/CaCl2
OCH3
CH3O
NH2
O
87
1. Triphosgene
2. CH3NH(OH)•HCl
OCH3
CH3O
CH3N(OH)CONH
O
88

Nonlimiting examples of dual function kadsurenone derivatives that can be prepared according to this process are:

Compound 88 (Hydroxyurea):
rac-5-allyl-3A-methoxy-3-methyl-2-[3'-(N-hydroxy-N-methylureidyl)-4'-methoxyphenyl]-2,3,3A,6-tetrahydro-6-oxobenzofuran;

Derivatives of Hydroxyurea 88:
rac-5-allyl-3A-methoxy-3-methyl-2-[3'-(N-hydroxy-N-propylureidyl)-4'-methoxyphenyl]-2,3,3A,6-tetrahydro-6-oxobenzofuran;

rac-5-allyl-3A-methoxy-3-methyl-2-[3'-(N-hydroxy-N-phenylureidyl)-4'-methoxyphenyl]-2,3,3A,6-tetrahydro-6-oxobenzofuran;

rac-5-allyl-3A-methoxy-3-methyl-2-[3'-(N-hydroxy-N-n-pentylureidyl)-4'-methoxyphenyl]-2,3,3A,6-tetrahydro-6-oxobenzofuran;

rac-5-allyl-3A-methoxy-3-methyl-2-[3'-(N-hydroxy-N-methylureidyl)-4'-methoxyphenyl]-2,3,3A,6-tetrahydro-6-oxobenzofuran;

rac-5-allyl-3A-methoxy-3-methyl-2-[3'-(N-hydroxy-N-propylureidyl)-4'-methoxyphenyl]-2,3,3A,6-tetrahydro-6-oxobenzofuran;

rac-5-allyl-3A-methoxy-3-methyl-2-[3'-(N-hydroxy-N-phenylureidyl)-4'-methoxyphenyl]-2,3,3A,6-tetrahydro-6-oxobenzofuran;

rac-5-allyl-3A-methoxy-3-methyl-2-[4'-(N-hydroxy-N-pentylureidyl)-3'-methoxyphenyl]-2,3,3A,6-tetrahydro-6-oxobenzofuran;

rac-5-allyl-3A-methoxy-3-methyl-2-[4'-(N-benzyl-N-hydroxyureidyl)-3'-methoxyphenyl]-2,3,3A,6-tetrahydro-6-oxobenzofuran;

rac-5-allyl-3A-methoxy-3-methyl-2-[4'-(N-n-butyl-N-hydroxyureidyl)-3'-methoxyphenyl]-2,3,3A,6-tetrahydro-6-oxobenzofuran;

rac-5-allyl-3A-methoxy-3-methyl-2-[4'-(N-hydroxy-N-n-propylamido)-3'-methoxyphenyl]-2,3,3A,6-tetrahydro-6-oxobenzofuran;

rac-5-allyl-3A-methoxy-3-methyl-2-[4'-(N-hydroxy-N-methylureidyl)-3'-methoxyphenyl]-2,3,3A,6-tetrahydro-6-oxobenzofuran;

rac-5-allyl-3A-methoxy-3-methyl-2-[4'-(N-hydroxy-N-propylureidyl)-3'-methoxyphenyl]-2,3,3A,6-tetrahydro-6-oxobenzofuran;

rac-5-allyl-3A-methoxy-3-methyl-2-[4'-(N-hydroxy-N-phenylureidyl)-3'-methoxyphenyl]-2,3,3A,6-tetrahydro-6-oxobenzo-furan;

Derivatives of Reverse Hydroxyurea of Compound 88:

rac-5-allyl-3A-methoxy-3-methyl-2-[3'-(N-hydroxy-N'-cyclopropylureidyl)-4'-methoxyphenyl]-2,3,3A,6-tetrahydro-6-oxobenzofuran;

rac-5-allyl-3A-methoxy-3-methyl-2-[3'-(N-hydroxy-N'-benzylureidyl)-4'-methoxyphenyl]-2,3,3A,6-tetrahydro-6-oxobenzofuran;

rac-5-allyl-3A-methoxy-3-methyl-2-[3'-(N-hydroxy-N'-n-butylureidyl)-4'-methoxyphenyl]-2,3,3A,6-tetrahydro-6-oxobenzofuran;

rac-5-allyl-3A-methoxy-3-methyl-2-[4'-(N-hydroxy-N'-cyclopropylureidyl)-3'-methoxyphenyl]-2,3,3A,6-tetrahydro-6-oxobenzofuran;

rac-5-allyl-3A-methoxy-3-methyl-2-[4'-(N-hydroxy-N'-benzylureidyl)-3'-methoxyphenyl]-2,3,3A,6-tetrahydro-6-oxobenzofuran;

rac-5-allyl-3A-methoxy-3-methyl-2-[4'-(N-hydroxy-N'-n-butylureidyl)-3'-methoxyphenyl]-2,3,3A,6-tetrahydro-6-oxobenzofuran;

Hydroxamic acid derivatives of Compound 88:

rac-5-allyl-3A-methoxy-3-methyl-2-[3'-(N-hydroxy-N-n-butylcarboxamido)-4'-methoxyphenyl]-2,3,3A,6-tetrahydro-6-oxobenzofuran;

rac-5-allyl-3A-methoxy-3-methyl-2-[3'-(N-hydroxy-N-cyclopropylcarboxamido)-4'-methoxyphenyl]-2,3,3A,6-tetrahydro-6-oxobenzofuran;

rac-5-allyl-3A-methoxy-3-methyl-2-[4'-(N-hydroxy-N-cyclopropylcarboxamido)-3'-methoxyphenyl]-2,3,3A,6-tetrahydro-6-oxobenzofuran;

Methylene Spacer Derivatives of Hydroxyurea 88:

rac-5-allyl-3A-methoxy-3-methyl-2-[3'-(N-hydroxy-N-methylureidylmethyl)-4'-methoxyphenyl]-2,3,3A,6-tetrahydro-6-oxobenzofuran;

rac-5-allyl-3A-methoxy-3-methyl-2-[3'-(N-hydroxy-N-phenylureidylmethyl)-4'-methoxyphenyl]-2,3,3A,6-tetrahydro-6-oxobenzofuran;

rac-5-allyl-3A-methoxy-3-methyl-2-[3'-(N-hydroxy-N-n-pentylureidylmethyl)-4'-methoxyphenyl]-2,3,3A,6-tetrahydro-6-oxobenzofuran;

rac-5-allyl-3A-methoxy-3-methyl-2-[4'-(N-hydroxy-N-methylureidylmethyl)-3'-methoxyphenyl]-2,3,3A,6-tetrahydro-6-oxobenzofuran;

rac-5-allyl-3A-methoxy-3-methyl-2-[4'-(N-hydroxy-N-phenylureidylmethyl)-3'-methoxyphenyl]-2,3,3A,6-tetrahydro-6-oxobenzofuran;

rac-5-allyl-3A-methoxy-3-methyl-2-[4'-(N-hydroxy-N-isopropylureidylmethyl)-3'-methoxyphenyl]-2,3,3A,6-tetrahydro-6-oxobenzofuran;

Methylene spacer derivatives of reverse hydroxyurea 88:

rac-5-allyl-3A-methoxy-3-methyl-2-[3'-(N-hydroxy-N'-methylureidylmethyl)-4'-methoxyphenyl]-2,3,3A,6-tetrahydro-6-oxobenzofuran;

rac-5-allyl-3A-methoxy-3-methyl-2-[3'-(N-hydroxy-N'-phenylureidylmethyl)-4'-methoxyphenyl]-2,3,3A,6-tetrahydro-6-oxobenzofuran;

rac-5-allyl-3A-methoxy-3-methyl-2-[3'-(N-hydroxy-N'-isopropylmethyl)-4'-methoxyphenyl]-2,3,3A,6-tetrahydro-6-oxobenzofuran;

rac-5-allyl-3A-methoxy-3-methyl-2-[4'-(N-hydroxy-N'-methylureidylmethyl)-3'-methoxyphenyl]-2,3,3A,6-tetrahydro-6-oxobenzofuran;

rac-5-allyl-3A-methoxy-3-methyl-2-[4'-(N-hydroxy-N'-phenylureidylmethyl)-3'-methoxyphenyl]-2,3,3A,6-tetrahydro-6-oxobenzofuran;

rac-5-allyl-3A-methoxy-3-methyl-2-[4'-(N-hydroxy-N'-isobutylureidylmethyl)-3'-methoxyphenyl]-2,3,3A,6-tetrahydro-6-oxobenzofuran;

Compound 81 (hydroxyurea):

rac-5-allyl-3A-methoxy-3-methyl-2-[3'-(N-hydroxy-N-methylureidylethoxy)-4'-methoxyphenyl]-2,3,3A,6-tetrahydro-6-oxobenzofuran;

Derivatives of hydroxyurea 81:

rac-5-allyl-3A-methoxy-3-methyl-2-[3'-(N-hydroxy-N-propylureidylethoxy)-4'-methoxyphenyl]-2,3,3A,6-tetrahydro-6-oxobenzofuran;

rac-5-allyl-3A-methoxy-3-methyl-2-[3'-(N-hydroxy-N-isobutylureidylethoxy)-4'-methoxyphenyl]-2,3,3A,6-tetrahydro-6-oxobenzofuran;

rac-5-allyl-3A-methoxy-3-methyl-2-[3'-(N-hydroxy-N-phenylureidylethoxy)-4'-methoxyphenyl]-2,3,3A,6-tetrahydro-6-oxobenzofuran;

rac-5-allyl-3A-methoxy-3-methyl-2-[3'-(N-hydroxy-N-methylureidylethoxy)-4'-methoxyphenyl]-2,3,3A,6-tetrahydro-6-oxobenzofuran;

rac-5-allyl-3A-methoxy-3-methyl-2-[3'-(N-hydroxy-N-isopropylureidylethoxy)-4'-methoxyphenyl]-2,3,3A,6-tetrahydro-6-oxobenzofuran;

rac-5-allyl-3A-methoxy-3-methyl-2-[3'-(N-hydroxy-N-phenylureidylethoxy)-4'-methoxyphenyl]-2,3,3A,6-tetrahydro-6-oxobenzofuran;

rac-5-allyl-3A-methoxy-3-methyl-2-[4'-(N-hydroxy-N-propylureidylethoxy)-3'-methoxyphenyl]-2,3,3A,6-tetrahydro-6-oxobenzofuran;

rac-5-allyl-3A-methoxy-3-methyl-2-[4'-(N-hydroxy-N-isobutylureidylethoxy)-3'-methoxyphenyl]-2,3,3A,6-tetrahydro-6-oxobenzofuran;

rac-5-allyl-3A-methoxy-3-methyl-2-[4'-(N-hydroxy-N-sec-propylureidylethoxy)-3'-methoxyphenyl]-2,3,3A,6-tetrahydro-6-oxobenzofuran;

rac-5-allyl-3A-methoxy-3-methyl-2-[4'-(N-hydroxy-N-isobutylcarboxamidoethoxy)-3'-methoxyphenyl]-2,3,3A,6-tetrahydro-6-oxobenzofuran;

rac-5-allyl-3A-methoxy-3-methyl-2-[4'-(N-ethyl-N-hydroxcarboxamidoethoxy)-3'-methoxyphenyl]-2,3,3A,6-tetrahydro-6-oxobenzofuran;

rac-5-allyl-3A-methoxy-3-methyl-2-[4'-(N-hydroxy-N-methylureidylethoxy)-3'-methoxyphenyl]-2,3,3A,6-tetrahydro-6-oxobenzofuran;

rac-5-allyl-3A-methoxy-3-methyl-2-[4'-(N-cyclopropyl-N-hydroxyureidylethoxy)-3'-methoxyphenyl]-2,3,3A,6-tetrahydro-6-oxobenzofuran;

rac-5-allyl-3A-methoxy-3-methyl-2-[4'-(N-benzyl-N-hydroxyureidylethoxy)-3'-methoxyphenyl]-2,3,3A,6-tetrahydro-6-oxobenzofuran;

Hydroxamic Acid Derivatives of Compound 81:

rac-5-allyl-3A-methoxy-3-methyl-2-[3'-(N-cyclopropyl-N-hydroxycarboxamido)-4'-methoxyphenyl]-2,3,3A,6-tetrahydro-6-oxobenzofuran;

rac-5-allyl-3A-methoxy-3-methyl-2-[3'-(N-butyl-N-hydroxycarboxamido)-4'-methoxyphenyl]-2,3,3A,6-tetrahydro-6-oxobenzofuran;

Derivatives of Reverse Hydroxyurea of Compound 81:
rac-5-allyl-3A-methoxy-3-methyl-2-[3'-(N'-cyclopropyl-N-hydroxy-ureidylethoxy)-4'-methoxyphenyl]-2,3,3A,6-tetrahydro-6-oxobenzofuran;

rac-5-allyl-3A-methoxy-3-methyl-2-[3'-(N-hydroxyureidylethoxy)-4'-methoxyphenyl]-2,3,3A,6-tetrahydro-6-oxobenzofuran;

rac -5-allyl-3A-methoxy-3-methyl-2-[3'-(N'-n-butyl-N-hydroxyureidylethoxy)-4'-methoxyphenyl]-2,3,3A,6-tetrahydro-6-oxobenzofuran;

rac-5-allyl-3A-methoxy-3-methyl-2-[4'-(N'-cyclopropyl-N-hydroxyureidylethoxy)-3'-methoxyphenyl]-2,3,3A,6-tetrahydro-6-oxobenzofuran;

rac-5-allyl-3A-methoxy-3-methyl-2-[4'-(N'-benzyl-N-hydroxyureidylethoxy)-3'-methoxyphenyl]-2,3,3A,6-tetrahydro-6-oxobenzofuran;

rac-5-allyl-3A-methoxy-3-methyl-2-[4'-(N'-n-butyl-N-hydroxyureidylethoxy)-3'-methoxyphenyl]-2,3,3A,6-tetrahydro-6-oxobenzofuran

Example 8: Dual Function Dioxabicyclo-[3.3.0]octanes

Dioxabicyclo[3.3.0]octanes with PAF receptor antagonist activity can be modified to exhibit 5-lipoxygenase inhibiting activity by the addition of an R^1 group to a bulk tolerating location on the molecule. Nonlimiting examples of dual function dioxabicyclo[3.3.0]octanes are illustrated in Figure 8. Nonlimiting examples of specific dioxabicyclo[3.3.0]octanes include:

rac-trans-2-[3',4'-dimethoxy-5'-(N-hydroxy-N-methylureidyl)phenyl]-6-(3",4",5"-trimethoxyphenyl)-1,5-dioxabicyclo[3.3.0]octane;

rac-trans-2-[3',4'-dimethoxy-5'-(N-hydroxy-N-phenylureidyl)phenyl]-6-(3",4",5"-trimethoxyphenyl)-1,5-dioxabicyclo-[3.3.0]octane;

rac-trans-2-[3',4'-dimethoxy-5'-(N-cyclopropyl-N-hydroxyureidyl)phenyl]-6-(3",4",5"-trimethoxyphenyl)-1,5-dioxabicyclo[3.3.0]octane;

rac-trans-2-[3',4'-dimethoxy-5'-(N-hydroxy-N'-methylureidyl)phenyl]-6-(3",4",5"-trimethoxyphenyl)-1,5-dioxabicyclo-[3.3.0]octane;

rac-trans-2-[3',4'-dimethoxy-5'-(N'-butyl-N-hydroxyureidyl)phenyl]-6-(3",4",5"-trimethoxyphenyl)-1,5-dioxabicyclo-[3.3.0]octane;

rac-trans-2-[3',4'-dimethoxy-5'-(N-hydroxy-N'-phenylureidyl)phenyl]-6-(3",4",5"-trimethoxyphenyl)-1,5-dioxabicyclo-[3.3.0]octane;

rac-trans-2-[3',4'-dimethoxy-5'-(N-hydroxy-N-methylureidylmethyl)phenyl]-6-(3",4",5"-trimethoxyphenyl)-1,5-dioxabicyclo[3.3.0]octane;

rac-trans-2-[3',4'-dimethoxy-5'-(N-hydroxy-N-phenylureidylmethyl)phenyl]-6-(3",4",5"-trimethoxyphenyl)-1,5-dioxa-bicyclo[3.3.0]octane;

rac-trans-2-[3',4'-dimethoxy-5'-(N-hydroxy-N-propylureidylmethyl)phenyl]-6-(3",4",5"-trimethoxyphenyl)-1,5-dioxabicyclo[3.3.0]octane;

rac-trans-2-[3',4'-dimethoxy-5'-(N-hydroxy-N'-

methylureidylmethyl)phenyl]-6-(3",4",5"-trimethoxyphenyl)-1,5-dioxabicyclo[3.3.0]octane;

rac-trans-2-[3',4'-dimethoxy-5'-(N'-butyl-N-hydroxyureidylmethyl)phenyl]-6-(3",4",5"-trimethoxyphenyl)-1,5-dioxabicyclo[3.3.0]octane; and

rac-trans-2-[3',4'-dimethoxy-5'-(N'-benzyl-N-hydroxyureidylmethyl)phenyl]-6-(3",4",5"-trimethoxyphenyl)-1,5-dioxabicyclo[3.3.0]octane.

Example 9: Dual Function Antagonists with Oxaalkane, Thioalkane, Quinolylmethyl Ether, and Amidohydroxyurea Moieties

Using the procedures described above for the preparation of oxaalkane, thioalkane, quinolylmethyloxy, and amidohydroxyurea moieties, a wide variety of dual function antoagonists can be prepared that have both PAF receptor antagonist activity and 5-lipoxygenase inhibiting activity.

Specific nonlimiting examples are listed below. The PAF receptor antagonist that is used as the starting material for the dual function antagonist follows the compound name in parenthesis.

4-{6-(2-chlorophenyl)-11-methylcyclopentyl-[1,5:4,5] thieno [3,2-f] [1,3] imidazolo [3,2-a]-[1,4]diazpi-n-3-ylmethyl}-4-methoxy-3,4,5,6-tetrahydro-2H-pyran [and 2H-thiopyran] (from compound 2).

5-[4-3(4-methoxy-3,4,5,6-tetrahydro-2H-pyra-4-nyl)-4,5-dimethoxyphenylethyl)phenyl]2,3-dihydroimidazo[2,1-a]isoquinoline (from compound 17) [and 2H-thiopyran analog.]

N-[4-(3-4-methoxy-3,4,5,6-tetrahydro-2H-pyra-4-nyl)phenoxymethyl)phenyl]-3-(3-pyridyl)1H,

3H pyrrolo[1,2-C]thiazole-7-carboxamide (from compound 28) [and 2H-thiopyran analog.]

N-[3-(4-methoxy-3,4,5,6-tetrahydro-2H-pyra-4-nyl)phenyl]-3-(3-pyridyl)1H,3H-pyrrolo[1,2-C]thiazole-7-carboxamide (from compound 28) [and 2H-thiopyran analog.]

[R-(E)]-6-(3-(4-methoxy-3,4,5,6-tetrahydro-2H-thiopyra-4-nyl)phenoxymethyl)-3-pentyl-1-methyl-2-indole-N-[1-methyl-4-(3-pyridyl)butyl]-2-propenamide (from compound 63).

6-(2-chlorophenyl)-3-(2-quinolylmethoxy-methyl-11-methylcyclopentyl[1,5:4,5]thieno[3,2-f][1,3]imidazolo[3,2-a] [1,4]-diazepine (from compound 2).

5-[4-(3-(2-quinolylmethoxymethyl)-4,5-dimethoxyphenylethyl)phenyl]-2,3-dihydroimidazo-[2,1-a]iscoquinoline (from compound 17).

N[4-(3-(2-quinolylmethoxymethyl)-phenyl]-3-(3-pyridyl) 1H,3H-pyrrolo[1,2-C]thiazole-7-carboxamide (from compound 28).

N-[4-(3-(2-quinolylmethoxy)-phenyl]-3-(3-pyridyl) 1H,3H-pyrrolo[1,2-C]thiazole-7-carboxamide

[R-(E)-6-(2-quinolylmethoxy)-3-pentyl-1-methyl-2-indole-N-[1-methyl-4-(3-pyridylbutyl]-2-propenamide

[R-(E)]-6-(2-quinolylmethoxymethyl)-3-pentyl-1methyl-2-indole-N-[I-methyl-4-(3-pyridyl)butyl]-2-propenamide (from compound 63).

Amidohydroxyureas can be prepared, for example, from amine compounds numbered 4, 13, 72, 24, 60, and 87.

6-(2-chlorophenyl)-3-(N^3-hydroxy-N-methyl ureidylacetyl)aminomethyl-11-methylcyclopentyl [1,5:4,5]thieno[3,2-f] [1,3]imidazolo[3,2-a] [1,4]-diazepine (from compound 4).

5-[4,5-dimethoxy-3-(N^3-hydroxy-N^3-methylureidylacetyl)amino)phenylethyl)phenyl]-2,3-

dihydroimidazo[2,1-a]isoquinoline (from compound 13).

5-[4,5-dimethoxy-3-(N^3-hydroxy-N^3-methyl-ureidylacetyl)aminomethyl)phenylethyl)phenyl]-2,3-dihydroimidazo[2,1-a]isoquinoline (compound 72).

N-(4-(N^3-hydroxy-N^3-butylureidylacetyl)amino phenyl)-3-(3-pyridyl)-1H-pyrrolo[1,2-C]thiazole-7-carboxymide (compound 24).

9R-(E)]-5-(N^3-hydroxy-N^3-ethylureidyl-acetyl)methylamino-3-entyl-1-methyl-2-indole-N-[10-methy-4-(3-pyridyl)butyl]-2-propenamide (compound 6).

rac-5-allyl-3-methoxy-3-methyl-2-[3-(N^3-hydroxy-N^3-butylureidylacetyl)amino-4-methoxyphenyl]-2,3,3A,6-tetrahydro-6-oxobenzofuran (from 63).

F. Stereochemistry

It is sometimes found that one or more enantiomers of a biologically active compound is more active, and perhaps less toxic, than other enantiomers of the same compound. Such enantiomerically enriched compounds are often preferred for pharmaceutical administration to humans. For example, it has been discovered that trans-2,5-diaryl tetrahydrothiophene and trans-2,5-diaryl tetrahydrofuran are often more active PAF receptor antagonists than their cis counterparts.

One of ordinary skill in the art can easily separate the enantiomers of the disclosed compounds using known procedures, and can evaluate the biological activity of the isolated enantiomer using methods disclosed herein or otherwise known. Through the use of chiral NMR shift reagents, polarimetry, or chiral HPLC, the optical enrichment of the compound can be determined.

Classical methods of resolution include a variety of physical and chemical techniques. Often the simplest and most efficient technique is fractional recrystallization.

When recrystallization fails to provide material of acceptable optical purity, other methods can be evaluated. If the compound is basic, one can use chiral acids that form diastereomeric mixtures that may possess significantly different solubility properties. Nonlimiting examples of chiral acids include malic acid, mandelic acid, dibenzoyl tartaric acid, 3-bromocamphor-8-sulfonic acid, 10-camphorsulfonic acid, and di-p-toluoyltartaric acid. Similarly, acylation of a free hydroxyl group with a chiral acid also results in the formation of diastereomeric mixtures whose physical properties may differ sufficiently to permit separation.

Small amounts of enantiomerically enriched compounds can be obtained or purified by passing the racemic mixture through an HPLC column that has been designed for chiral separations, including cyclodextrin bonded columns marketed by Rainin Corporation.

II. Evaluation of Biological Activity

A wide variety of biological assays have been used to evaluate the ability of a compound to act as a PAF receptor antagonist, including the ability of the compound to bind to PAF receptors, and the effect of the compound on various PAF mediated pathways. Any of these known assays can be used to evaluate the ability of the compounds disclosed herein to act as PAF receptor antagonists.

For example, PAF is known to induce hemoconcentration and increased permeability of

microcirculation leading to a decrease in plasma volume. PAF mediated acute circulatory collapse can be used as the basis of an assay to evaluate the ability of a compound to act as a PAF antagonist, by analyzing the effect of the compound on PAF induced decreased plasma volume in an animal model such as mouse.

Endotoxemia causes the release of chemical mediators including eicosanoids, PAF, and tumor necrosis factor (TNF) that stimulate a variety of physiologic responses including fever, hypotension, leukocytosis, and disturbances in glucose and lipid metabolism. Endotoxemia can result in severe shock and death. Endotoxin-induced mouse mortality is a useful animal model to evaluate the pharmacological effect of compounds on endotoxic shock.

Two other common assays used to evaluate the ability of a compound to act as a PAF receptor antagonist are platelet aggregation in vitro and hypotension in rats (Shen, *et al.*, "The Chemical and Biological Properties of PAF Agonists, Antagonists, and Biosynthetic Inhibitors", Platelet-Activating Factor and Related Lipid Mediators, F. Snyder, Ed. Plenum Press, New York, NY 153 (1987).)

A wide variety of biological assays have also been used to evaluate the ability of a compound to inhibit the enzyme 5-lipoxygenase. For example, a cytosol 5-lipoxygenase of rat basophilic leukemia cells (RBL) has been widely utilized in studies on leukotriene biosynthesis. Compounds that inhibit 5-lipoxygenase decrease the levels of leukotrienes.

Another biological assay used to evaluate the ability of a compound to inhibit the enzyme 5-lipoxygenase is based on the classic pharmacological model of inflammation induced by

the topical application of arachidonic acid to the mouse ear. On application, arachidonic acid is converted by 5-lipoxygenase to various leukotrienes (and other mediators), which induce changes in blood flow, erythema, and increase vasodilation and vasopermeability. The resulting edema is measured by comparing the thickness of the treated ear to a control ear. Agents that inhibit 5-lipoxygenase reduce the edematous response, by lowering the amounts of biochemical mediators formed from arachidonic acid.

Detailed procedures for assays that can be used to evaluate the PAF and 5-lipoxygenase inhibiting activity of the compounds disclosed herein are provided below.

Example 10: Ability of Dual Function Antagonist to Bind to PAF Receptors

a) Preparation of Human Platelet Membranes:

Human platelet membranes can be prepared from platelet concentrates obtained from the American Red Cross Blood Services (Dedham, MA). After several washes with platelet wash solution (150 mM NaCl, 10 mM Tris, and 2 mM EDTA, pH 7.5), the platelet pellets are resuspended in 5 mM $MgCl_2$, 10 mM Tris, and 2 mM EDTA at pH 7.0. The cells are then quickly frozen with liquid nitrogen and thawed slowly at room temperature. The freezing and thawing procedure should be repeated at least three times. For further fractionation of membrane fragments, the lysed membrane suspension is layered over the top of a discontinuous sucrose density gradient of 0.25, 1.03, and 1.5 M sucrose prepared in 10 mM $MgCl_2$, 10 mM Tris and 2 mM EDTA, pH 7.0, and centrifuged at 63,500 x g for 2 hr. The membrane fractions banding between 0.25 and 1.03 M (membrane A) and between 1.03 and 1.5 M (membrane

B) are collected separately. The protein concentration of the membrane preparations is determined by Lowry's method with bovine serum albumin (BSA) as the standard. The membranes are then separated into smaller fractions (4 ml each) and stored at -80° C and thawed before use.

b) [^{3}H]PAF Binding inhibition:

The ability of [^{3}H]PAF to bind to specific receptors on human platelet membranes is evaluated at optimal conditions at pH 7.0 and in the presence of 10 mM $MgCl_2$. Membrane protein (100 ug) is added to a final 0.5 ml solution containing 0.15 pmol (0.3 nM concentration) of [^{3}H]PAF and a known amount of unlabeled PAF or PAF receptor antagonist in 10 mM $MgCl_2$, 10 mM Tris and 0.25% BSA at pH 7.0. After incubation for four hours at 0°C, the bound and unbound [^{3}H]PAF is then separated through a Whatman GF/C glass fiber filter under vacuum. No degradation of filter bound [^{3}H]PAF has been detected under this assay condition. The nonspecific binding is defined as the total binding in the presence of excess unlabeled PAF (1 mM) where no further displacement is found with higher concentrations of either unlabeled PAF or PAF analogs or PAF receptor antagonists. The specific binding is defined as the difference between total binding and nonspecific binding.

To determine the relative potency of tested compounds, [^{3}H]PAF binding in the presence of inhibitors is normalized in terms of percent inhibition by assigning the total binding in the absence of inhibitors as 0% inhibition and the total binding in the presence of 1 mM unlabeled PAF as 100%. The percent inhibition by the compound can be calculated by the formula expressed below:

% inhibition = [(Total binding - total binding in the presence of compound)/nonspecific binding] x 100%

The IC_{50} is calculated as the concentration of the inhibitor necessary to obtain 50% inhibition of the specific [^{3}H]PAF binding and is calculated by a nonlinear regression computer software program, GraphPad Inplot, version 3.0 (GraphPad software, San Diego, CA).

Example 11: Effect of Compound on PAF-induced Hemoconcentration

a) Animals

Female CD-1 mice, weighing 16-20 grams, can be obtained from Charles River Laboratory (Wilmington, MA). Tap water and rodent laboratory chow (5001, Purina Mills, St. Louis, MO) should be provided ad libitum, and the mice housed for an average of four days prior to use.

b) Hematocrit measurement

PAF (1-O-alkyl-2-acetyl-*sn*-glyceryl-3-phosphorylcholine, Sigma Chemical Co.) is dissolved in 0.25% bovine serum albumin (BSA) in 0.9% NaCl solution. Except for dose-response studies, 10 μg (10 ml/kg) of PAF solution is injected into the tail vein. Test compounds are dissolved in 0.5 DMSO saline solution and intravenously injected at 3 mg/kg body weight 15 minutes prior to PAF challenge. Thirty to fifty μL blood is collected by cutting the tail end into a heparinized micro-hematocrit tube (O.D. 1.50 mm) 15 minutes after PAF administration.

Example 12: Effect of Compounds on Arachidonic Acid-induced Mouse Ear Edema

a) Animals

The animals are obtained and treated as in Example 10 above.

b) Edema measurement

Arachidonic acid is applied to both ears of mice in 0.025 ml of freshly prepared vehicle (acetone:pyridine:water (97:2:1 v/v/v) and dried under a Sun-Lite Hitensity bulb. Except for dose-response studies, 0.5 mg of arachidonic acid is used for all applications. All test compounds are dissolved in 0.5% DMSO saline solution and intravenously injected at 3 mg/kg body weight 15 minutes prior to arachidonic acid treatment. Animals are sacrificed by cervical dislocation at 1 hour after topical application of arachidonic acid. A 7 mm-diameter disc of tissue is removed from each ear by means of a metal punch. Edema is measured by the average wet weight of the both ear tissues.

Example 13: Effect of Compounds on Endotoxin-induced Mouse Mortality

a) Animals

The mice are obtained and treated as in Example 10 above.

b) Mortality Measurement

Endotoxin (E. coli serotype 0127:B8, lipopolysaccharide, Sigma Chemical Co.) St. Louis, is freshly dissolved in 0.9% NaCl solution. Except for dose-response studies, endotoxin at 50 mg/kg is injected into the tail vein. Test compounds are dissolved in 0.5% DMSO saline solution and intravenously injected at 3 mg/kg body weight 15 minutes prior to PAF challenge. Death occurs

typically within 12-36 hours. Mortality is recorded 48 hours after endotoxin challenge, as death rarely occurs after 48 hr. The extent of mouse mortality in response to varying concentrations of endotoxin within 48 hours after intravenous injection of endotoxin is evaluated.

Example 14: Effect of Compounds on Cytosol 5-Lipoxygenase of Rat Basophile Leukemia Cells

a) Enzyme preparation

Washed rat RBL cells (4x108) are suspended in 20 ml of 50 M potassium phosphate buffer at pH 7.4 containing 10% ethylene glycol/1 mM EDTA (Buffer A). The cell suspension is sonicated at 20 KHz for 30 seconds, and the sonicate centrifuged at 10000 x g for 10 minutes, followed by further centrifugation at 105000 x g for 1 hr. The supernatant solution (cytosol fraction) containing 5-lipoxygenase is stored at - 70°C. Protein concentration is determined according to the procedure of Bradford (Bradford Dye Reagent) with bovine serum albumin as a standard.

b) Enzyme assay

For routine assay of 5-LO the mixture should contain 50 mM potassium phosphate buffer at pH 7.4, 2 mM $CaCl_2$, 2 mM ATP, 25 M arachidonic acid (0.1 Ci) and enzyme (50-100 mg of protein) in a final volume of 200 L. The reaction is carried out at 24°C for 3 minutes. The mixture is extracted with 0.2 ml of an ice-cold mixture of ethyl ether:methanol: 0.2 M citric acid (30:4:1). The extract is subjected to thin-layer chromatography at -10°C in a solvent system of petroleum ether:ethyl ether:acetic acid (15:85:0.1). The silica gel zones corresponding to authentic

arachidonic acid and its metabolites are scrapped into scintillation vials for counting. The enzyme activity is expressed in terms of the amount of arachidonic acid oxygenated for 3 minutes.

III. Pharmaceutical Compositions

Humans, equine, canine, bovine and other animals, and in particular, mammals, suffering from disorders mediated by PAF or products of 5-lipoxygenase can be treated by administering to the patient an effective amount of one or more of the above-identified compounds or a pharmaceutically acceptable derivative or salt thereof in a pharmaceutically acceptable carrier or diluent. The active materials can be administered by any appropriate route, for example, orally, parenterally, intravenously, intradermally, subcutaneously, or topically, in liquid, cream, gel or solid form.

As used herein, the term pharmaceutically acceptable salts or complexes refers to salts or complexes that retain the desired biological activity of the above-identified compounds and exhibit minimal undesired toxicological effects. Nonlimiting examples of such salts are (a) acid addition salts formed with inorganic acids (for example, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, and the like), and salts formed with organic acids such as acetic acid, oxalic acid, tartaric acid, succinic acid, malic acid, ascorbic acid, benzoic acid, tannic acid, pamoic acid, alginic acid, polyglutamic acid, naphthalenesulfonic acid, naphthalenedisulfonic acid, and polygalacturonic acid; (b) base addition salts formed with polyvalent metal cations such as zinc, calcium, bismuth, barium, magnesium, aluminum, copper,

cobalt, nickel, cadmium, sodium, potassium, and the like, or with an organic cation formed from N,N-dibenzylethylene-diamine, D-glucosamine, ammonium, tetraethylammonium, or ethylenediamine; or (c) combinations of (a) and (b); e.g., a zinc tannate salt or the like.

The active compound is included in the pharmaceutically acceptable carrier or diluent in an amount sufficient to deliver to a patient a therapeutically effective amount without causing serious toxic effects in the patient treated. A preferred dose of the active compound for all of the above-mentioned conditions is in the range from about 0.01 to 300 mg/kg, preferably 0.1 to 100 mg/kg per day, more generally 0.5 to about 25 mg per kilogram body weight of the recipient per day. A typical topical dosage will range from 0.01 - 3% wt/wt in a suitable carrier. The effective dosage range of the pharmaceutically acceptable derivatives can be calculated based on the weight of the parent compound to be delivered. If the derivative exhibits activity in itself, the effective dosage can be estimated as above using the weight of the derivative, or by other means known to those skilled in the art.

The compound is conveniently administered in any suitable unit dosage form, including but not limited to one containing 1 to 3000 mg, preferably 5 to 500 mg of active ingredient per unit dosage form. A oral dosage of 25-250 mg is usually convenient.

The active ingredient should be administered to achieve peak plasma concentrations of the active compound of about 0.01 -30 μM, preferably about 0.1-10 μM. This may be achieved, for example, by the intravenous injection of a solution or formulation of the active ingredient,

optionally in saline, or an aqueous medium or administered as a bolus of the active ingredient.

The concentration of active compound in the drug composition will depend on absorption, distribution, inactivation, and excretion rates of the drug as well as other factors known to those of skill in the art. It is to be noted that dosage values will also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that the concentration ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed composition. The active ingredient may be administered at once, or may be divided into a number of smaller doses to be administered at varying intervals of time.

Oral compositions will generally include an inert diluent or an edible carrier. They may be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition.

The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic

acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring. When the dosage unit form is a capsule, it can contain, in addition to material of the above type, a liquid carrier such as a fatty oil. In addition, dosage unit forms can contain various other materials which modify the physical form of the dosage unit, for example, coatings of sugar, shellac, or other enteric agents.

The active compound or pharmaceutically acceptable salt or derivative thereof can be administered as a component of an elixir, suspension, syrup, wafer, chewing gum or the like. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors.

The active compound or pharmaceutically acceptable derivatives or salts thereof can also be mixed with other active materials that do not impair the desired action, or with materials that supplement the desired action, such as antibiotics, antifungals, antiinflammatories, or antiviral compounds.

Solutions or suspensions used for parenteral, intradermal, subcutaneous, or topical application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers

such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. The parental preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

If administered intravenously, preferred carriers are physiological saline or phosphate buffered saline (PBS).

In one embodiment, the active compounds are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc.

Liposomal suspensions may also be pharmaceutically acceptable carriers. These may be prepared according to methods known to those skilled in the art, for example, as described in U.S. Patent No. 4,522,811 (which is incorporated herein by reference in its entirety). For example, liposome formulations may be prepared by dissolving appropriate lipid(s) (such as stearoyl phosphatidyl ethanolamine, stearoyl phosphatidyl choline, arachadoyl phosphatidyl choline, and cholesterol) in an inorganic solvent that is then evaporated, leaving behind a thin film of dried lipid on the surface of the container. An aqueous solution of the active compound or its monophosphate, diphosphate, and/or triphosphate derivatives are then introduced into the container. The container

is then swirled by hand to free lipid material from the sides of the container and to disperse lipid aggregates, thereby forming the liposomal suspension.

Modifications and variations of the present invention relating to compounds that act as PAF receptor antagonists and inhibitors 5-lipoxygenase methods for the treatment of disorders mediated by platelet activating factor and products of 5-lipoxygenase, will be obvious to those skilled in the art from the foregoing detailed description of the invention. Such modifications and variations are intended to come within the scope of the appended claims.

We claim.

1. A method for imparting 5-lipoxygenase inhibiting activity to a compound that is a PAF receptor antagonist to provide a dual function antagonist, comprising the addition of R^1 to a bulk tolerating location on the compound, wherein R^1 is:

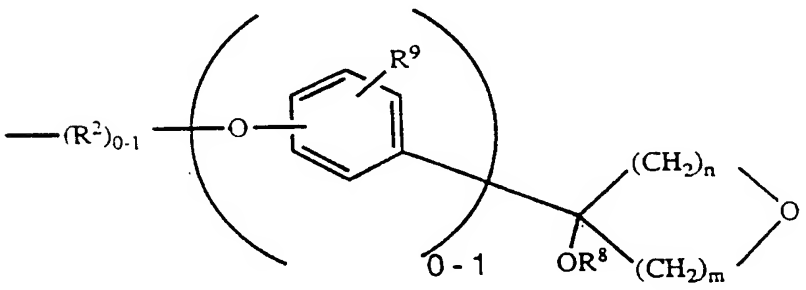
(1) a hydroxamate or hydroxyurea of the formula:

$-R^2N(OM)C(O)N(R^3)R^4$, $-R^2N(R^3)C(O)N(OM)R^4$,
$-R^2N(OM)C(O)R^4$, $-R^2C(O)N(OM)R^4$, $-N(OM)C(O)N(R^3)R^4$,
$-N(R^3)C(O)N(OM)R^4$, $-N(OM)C(O)R^4$, or $-C(O)N(OM)R^4$;

(2) an amidohydroxyurea of the formula:

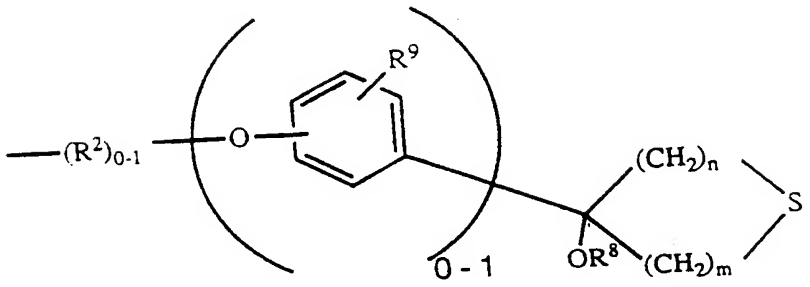
$-N(R^8)C(O)C(R^8)N(OM)C(O)NHR^9$,
$-C(O)N(R^8)C(R^8)N(OM)C(O)NHR^9$,
$-R^2N(R^8)C(O)C(R^8)N(OM)C(O)NHR^9$,
$-R^2C(O)N(R^8)C(R^8)N(OM)C(O)NHR^9$,
$-NHC(O)N(OM)C(R^8)C(O)N(R^8)_2$; or
$-NHC(O)N(OM)C(R^8)N(R^8)C(O)R^8$;

(3) an oxalkane of the structure:

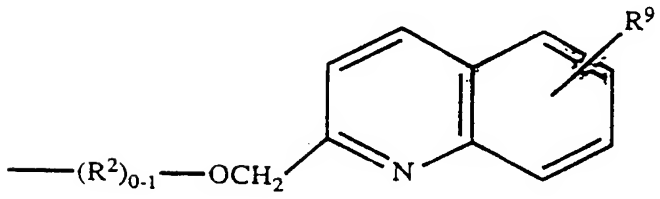


wherein n and m are independently 1-4 ;

(4) a thioalkane of the structure:



or (5) a quinolylmethoxy of the structure:



wherein:

R^2 is alkyl, alkenyl, alkynyl, alkyaryl, aralkyl, halo lower alkyl, halo lower alkyl, halo lower alkynyl, $-C^{1-10}$alkyl(oxy)C^{1-10}alkyl, $-C^{1-10}$alkyl(thio)C^{1-10}alkyl, $-N(R^3)C(O)$alkyl, $-N(R^3)C(O)$alkenyl, $-N(R^3)C(O)$alkynyl, $-N(R^3)C(O)$(alkyl)oxy(alkyl), $-N(R^3)C(O)$(alkyl)thio(alkyl), $-N(R^3)C(O)N$(alkyl), $-N(R^3)C(O)N$(alkenyl), $-N(R^3)C(O)N$(alkynyl), $-N(R^3)C(O)N$(alkyl)oxy(alkyl), $-N(R^3)C(O)N$(alkyl)thio(alkyl), $-N(R^3)C(O_2)$alkyl, $-N(R^3)C(O_2)$alkenyl, $-N(R^3)C(O_2)$alkynyl, $-N(R^3)C(O^2)$(alkyl)oxy(alkyl),

$-N(R^3)C(O_2)(alkyl)thio(alkyl)$, $-OC(O_2)alkyl$, $-OC(O_2)alkenyl$, $-OC(O_2)alkynyl$, $-OC(O_2)(alkyl)oxy(alkyl)$, $-OC(O_2)(alkyl)thio(alkyl)$, $-N(R^3)C(S)alkyl$, $-N(R^3)C(S)alkenyl$, $-N(R^3)C(S)alkynyl$, $-N(R^3)C(S)(alkyl)oxy(alkyl)$, $-N(R^3)C(S)(alkyl)thio(alkyl)$, $-N(R^3)C(S)N(alkyl)$, $-N(R^3)C(S)N(alkenyl)$, $-N(R^3)C(S)N(alkynyl)$, $-N(R^3)C(S)N(alkyl)oxy(alkyl)$, $-N(R^3)C(S)N(alkyl)thio(alkyl)$, $-N(R^3)C(S)S(alkyl)$, $-N(R^3)C(S)S(alkenyl)$, $-N(R^3)C(S)S(alkynyl)$, $-N(R^3)C(S)S(alkyl)oxy(alkyl)$, $-N(R^3)C(S)S(alkyl)thio(alkyl)$, $-SC(S)S(alkyl)$, $-SC(S)S(alkenyl)$, $-SC(S)S(alkynyl)$, $-SC(S)S(alkyl)oxy(alkyl)$, or $-SC(S)S(alkyl)thio(alkyl)$;

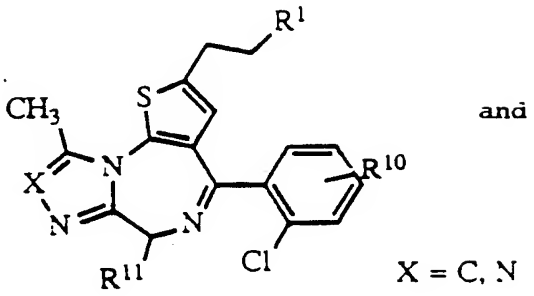
R^3 and R^4 are independently alkyl, alkenyl, alkynyl, aryl, aralkyl, alkyaryl, hydrogen, C_{1-6} alkoxy-C_{1-10} alkyl, C_{1-6} alkylthio-C_{1-10} alkyl, and C_{1-10} substituted alkyl (wherein the substituent is independently hydroxy or carbonyl, located on any of C_{1-10});

R^8 is H, lower alkyl, or lower alkenyl;

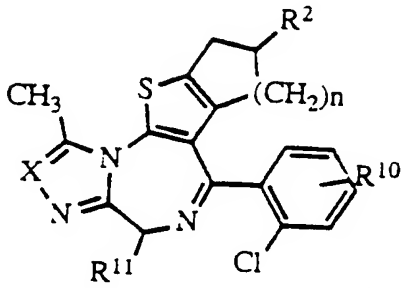
R^9 is H, halogen, lower alkoxy, or lower alkyl; and

M is hydrogen, a pharmaceutically acceptable cation, or a metabolically cleavable leaving group.

2. The method of claim 1, wherein the dual function antagonist is selected from the group consisting of:



and

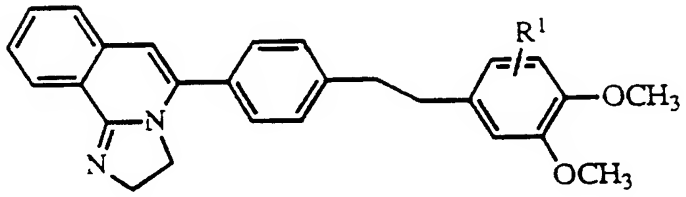


X = C, N

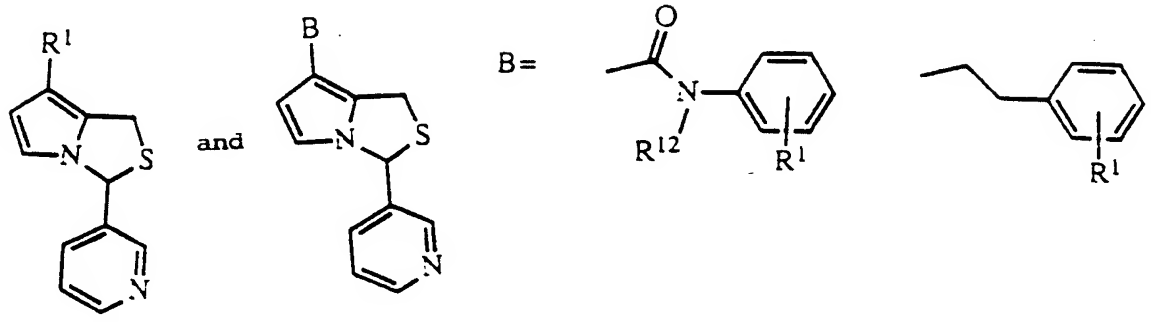
n = 1,2

X = C, N

3. The method of claim 1, wherein the dual function antagonist has the structure:

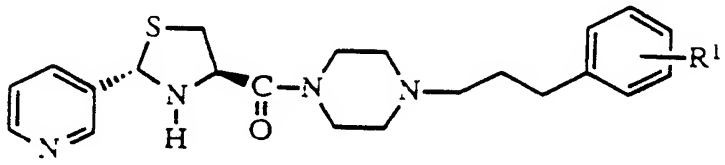


4. The method of claim 1, wherein the dual function antagonist is selected from the group consisting of:

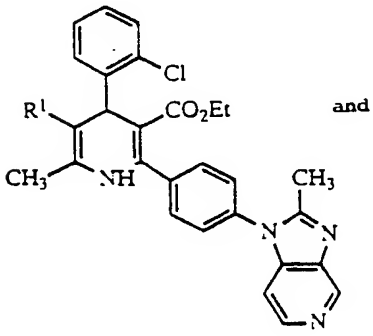


R^{12} is H, alkyl, aryl, or aralkyl.

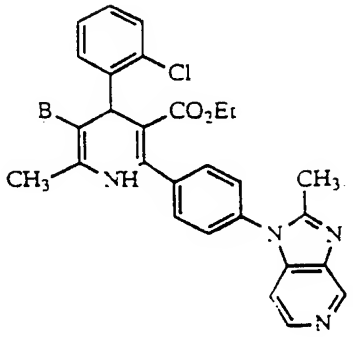
5. The method of claim 1, wherein the dual function antagonist has the structure:



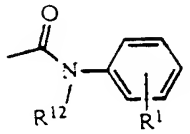
6. The method of claim 1, wherein the dual function antagonist is selected from the group consisting of:

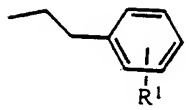


and



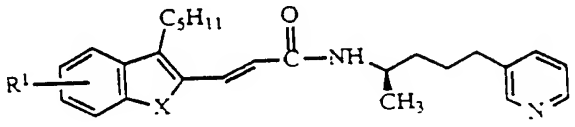
B=

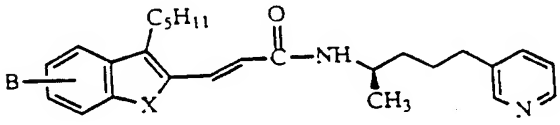




R^{12} is H, alkyl, aryl, or aralkyl

7. The method of claim 1, wherein the dual function antagonist is selected from the group consisting of:

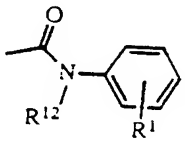


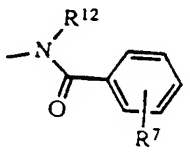


X = S, NCH_3

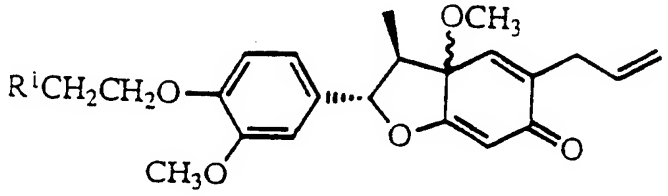
R^{12} is H, alkyl, aryl, or aralkyl.

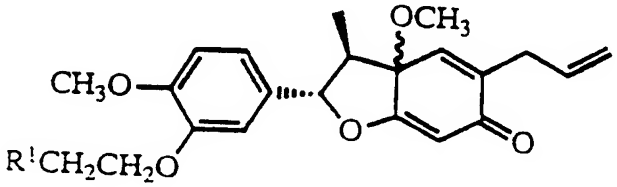
B=



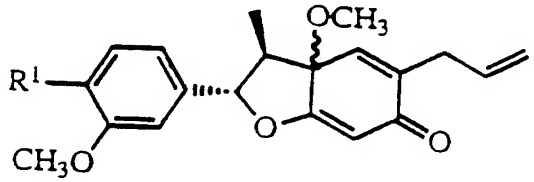


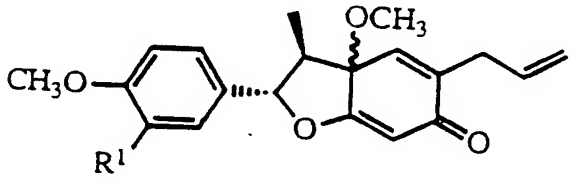
8. The method of claim 1, wherein the dual function antagonist is selected from the group consisting of:



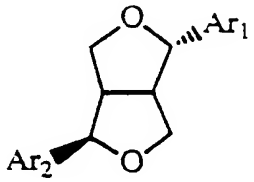


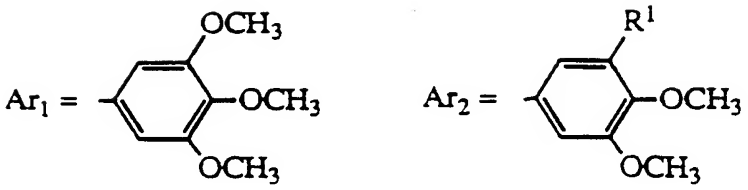
9. The method of claim 1, wherein the dual function antagonist is selected from the group consisting of:





10. The method of claim 1, wherein the dual function antagonist has the structure:





11. The dual function antagonist of claim 3.

12. The dual function antagonist of claim 4.

13. The dual function antagonist of claim 5.

14. The dual function antagonist of claim 6.

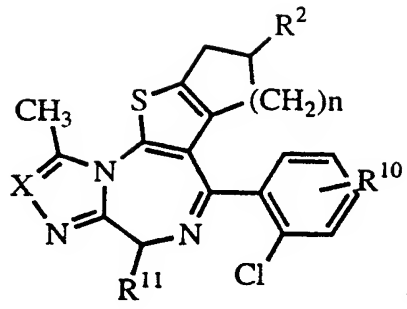
15. The dual function antagonist of claim 7.

16. The dual function antagonist of claim 8.

17. The dual function antagonist of claim 9.

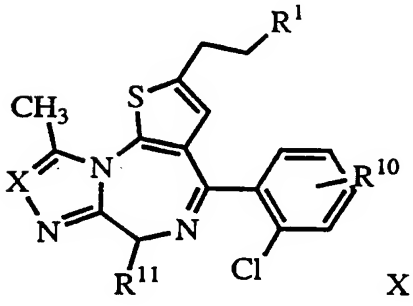
18. The dual function antagonist of claim 10.

19. The dual function antagonist of claim 11.



n = 1,2

X = C, N



X = C, N

Figure 1

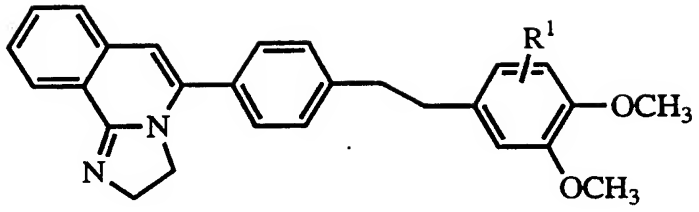


Figure 2

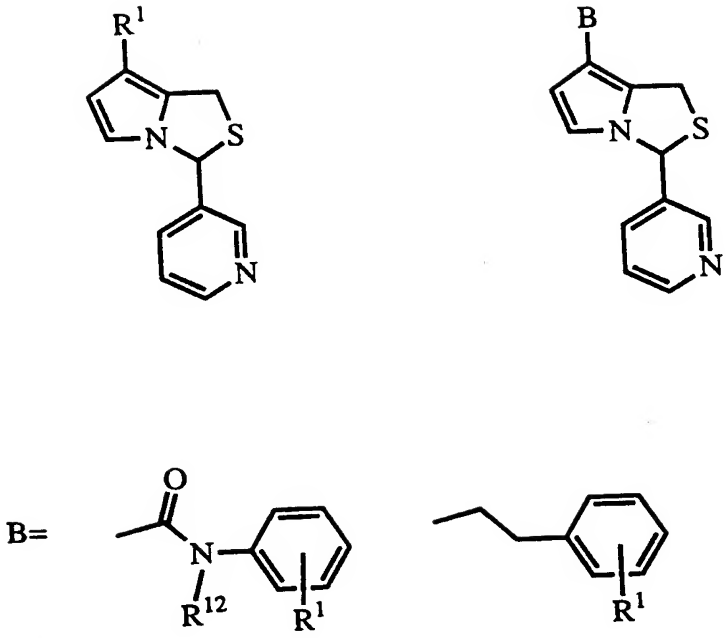


Figure 3

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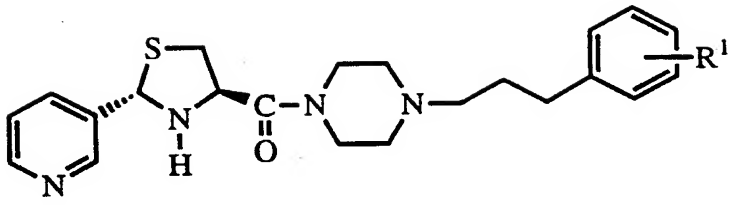

Figure 4

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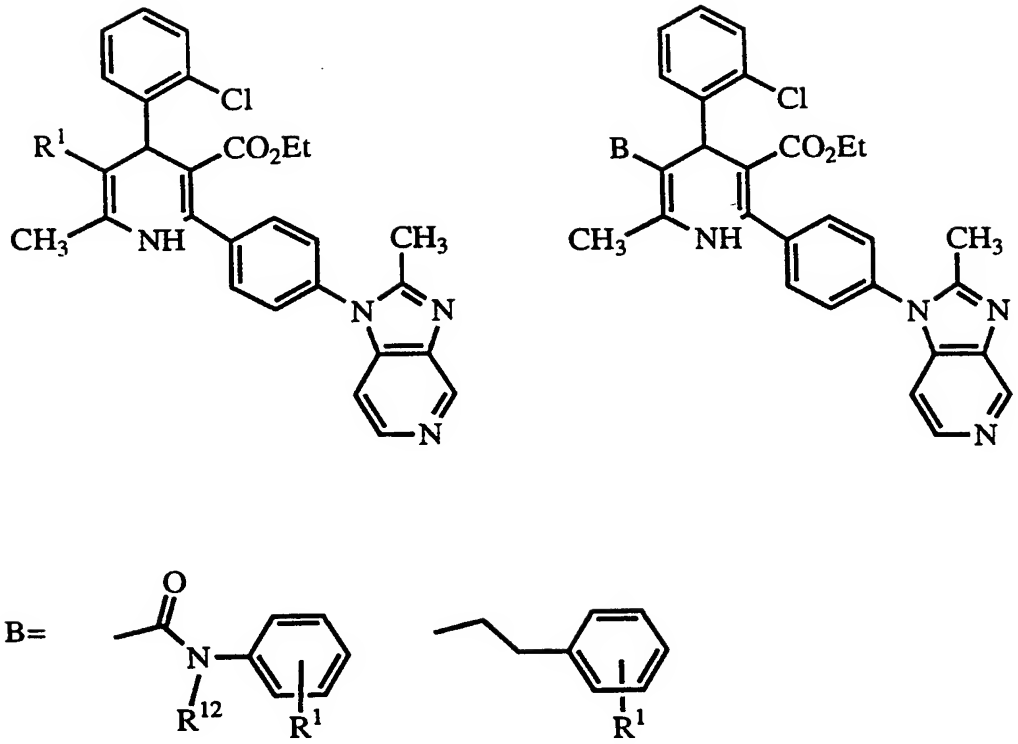
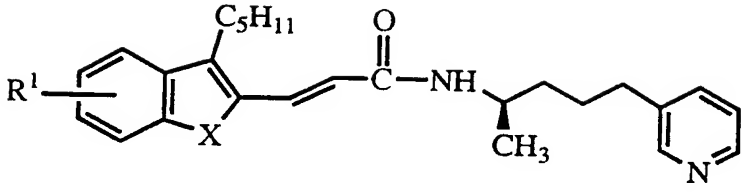
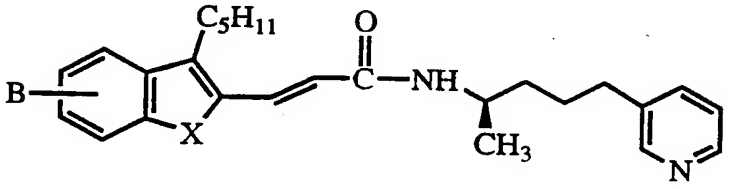


Figure 5





X = S, NCH_3

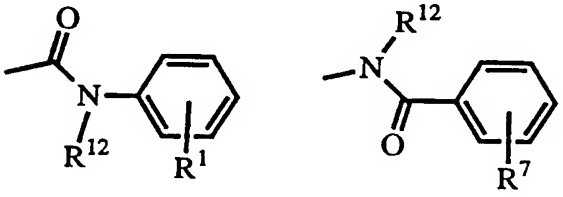
B= 

Figure 6

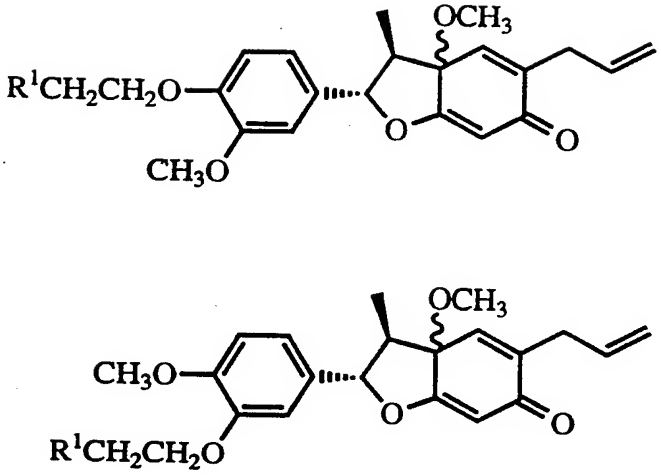


Figure 7

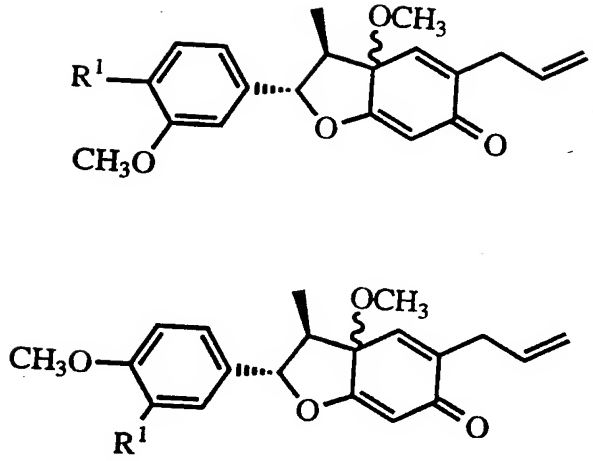


Figure 7a

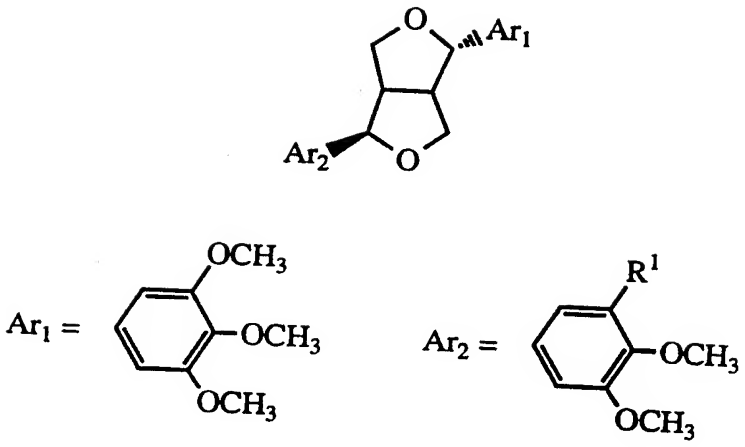


Figure 8